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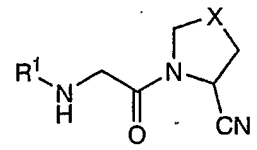
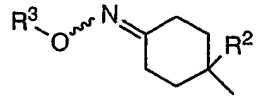
(54) Title: 2-CYANOPYRROLIDINE DERIVATIVES AND THEIR USE AS DPP-IV INHIBITORS



(I)



(II)

(57) Abstract: A compound of the formula (I) or a pharmaceutically acceptable salt thereof: [wherein X is CFH, or CF?2#191, R¿1? is the moiety represented by the formula: [wherein R¿2? is (lower)alkyl, R¿3? is phenyl-(lower)alkyl, and the like.], and the like.] Compounds of formula (I) inhibit DPP-IV activity. They are therefore useful in the treatment of conditions mediated by DPP-IV, such as NIDDM.

DESCRIPTION

2-CYANOPYRROLIDINE DERIVATIVES AND THEIR USE AS DPP-IV INHIBITORS

TECHNICAL FIELD

This invention relates to the compounds and pharmaceutically acceptable salts thereof which inhibit dipeptidyl peptidase-IV (DPP-IV).

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above-mentioned compounds or pharmaceutically acceptable salts thereof as an active ingredient, a method for treatment and/or prevention of NIDDM, or the like, and use of the above compound.

BACKGROUND ART

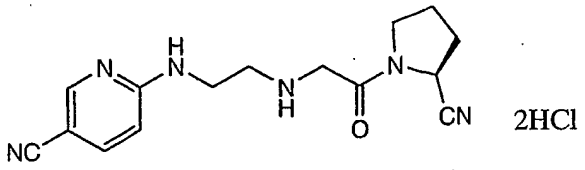
It is known that DPP-IV has various physiological functions in living body, especially has the action which inactivates Glucagon-like peptide-1 (GLP-1) by cleaving the terminal dipeptide (His-Ala). That is, the resultant peptide is the receptor antagonist of GLP-1 and totally reduces the activity of GLP-1.

This GLP-1 has very important role in sugar metabolism. For example, (1) GLP-1 intensifies the secretion of insulin, (2) express genes which are indispensable for the secretion of insulin, (3) stimulate proliferation of β-cell, (4) suppresses secretion of glucagon, (5) suppresses the function about secretion and motility of digestive organs (especially, peristalsis), and (6) suppresses appetite. That is, GLP-1 restricts food ingestion, postpones the process of digestion and absorption, and raised the use of the sugar in blood.

Therefore, the inhibitor of DPP-IV can maintain the activity of GLP-1, so it is expected as a medicine to treat and prevent various diseases, especially non-insulin

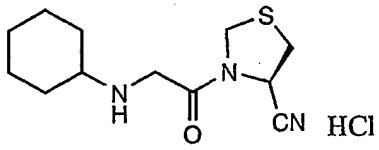
dependent diabetes mellitus (NIDDM).

Hitherto, such inhibitors of DPP-IV are known so far. For example, in US 6,011,155, 2-cyanopyrrolidine compounds like following are disclosed.



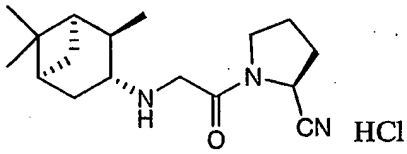
Pyrrolidine, 1-[[2-[(5-cyano-2-pyridinyl)amino]ethyl]amino]actyl-2-cyano, (S)-, monohydrochloride

In US 6,110,949, 4-cyanothiazolidine compounds like following are disclosed.



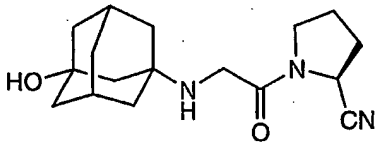
3-[(Cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine monohydrochloride

In US 6,124,305, 2-cyanopyrrolidine compounds like following are disclosed.



Pyrrolidine, 1-[(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)amino]acetyl-2-cyano, (S)[1S[1α,2β,3α(S),5α]] monohydrochloride

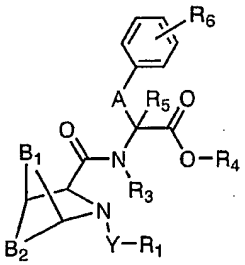
In WO 00/34241, 2-cyanopyrrolidine compounds like following are disclosed.



"LAF-237"
Pyrrolidine, 1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano, (S)

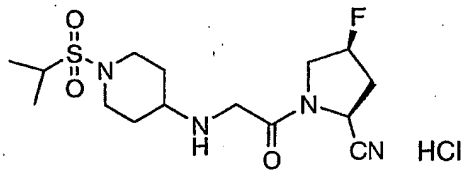
WO 02/02556 discloses following compounds as α4

integrin receptor antagonists for treating integrin mediated disorder such as asthma, rheumatoid arthritis, or the like.



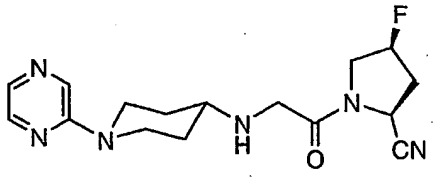
In the above formula, R_3 and R_5 may be bonded to form a pyrrolidine ring. However, such compound or compounds, which has hydrophilic group on azabicyclo moiety, are not described specifically.

WO 03/002553 discloses (2S,4S)-4-fluoro-1-({[1-(isopropylsulfonyl)-4-piperidinyl]amino}acetyl)-2-pyrrolidinecarbonitrile hydrochloride.



However, the other pyrrolidinecarbonitrile compounds substituted by [(lower)alkyl]sulfonyl group are not described.

WO 03/074500 discloses (2S,4S)-4-fluoro-1-(2-{[1-(2-pyrazinyl)piperidin-4-yl]amino}acetyl)-2-pyrrolidinecarbonitrile.



DISCLOSURE OF INVENTION

Under the above situation, the inventors of this invention found that the introduction of the oxime derivative group at appropriate position of the compound

result in remarkable improvement of the activity to inhibit DPP-IV, and completed this invention.

Accordingly, this invention relates to DPP-IV inhibitor. More particularly, this invention relates to DPP-IV inhibitor useful for treating or preventing conditions mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

That is, one object of this invention is to provide new compounds and pharmaceutically acceptable salts thereof, of which activity to inhibit DPP-IV is remarkably improved against known compounds.

Another object of this invention is to provide a medicament and pharmaceutical composition containing the compound(s) and/or pharmaceutically acceptable salts thereof as an active ingredient.

A further object of this invention is to provide a method for inhibiting DPP-IV comprising administering an effective amount of the compounds and/or pharmaceutically acceptable salts thereof.

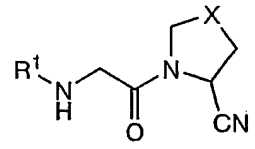
A further object of this invention is to provide a use of the compounds and pharmaceutically acceptable salts thereof as medicaments.

A further object of this invention is to provide the compounds and pharmaceutically acceptable salts thereof which are useful for the manufacture of medicaments for treating or preventing conditions mediated by DPP-IV inhibition, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus,

especially NIDDM.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the new compound.

The compounds of this invention can be represented by the following formula (I):

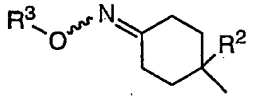


(I)

[wherein

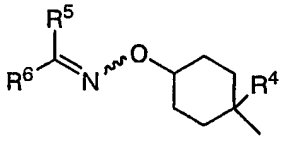
X is CFH, or CF_2,

R^1 is the moiety represented by the formula:



[wherein R^2 is (lower)alkyl,

R^3 is cycloalkyl, aryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group)], or

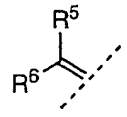


the moiety represented by the formula:

[wherein R^4 is (lower)alkyl,

R^5 is hydrogen, or (lower)alkyl,

R^6 is (lower)alkyl, cycloalkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), and

the partial structure:  may form cycloalkylidene],

the "substituent(s)" is(are) selected from the group consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy, halogen, cyano, nitro, amino and hydroxy]

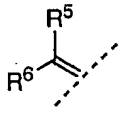
In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

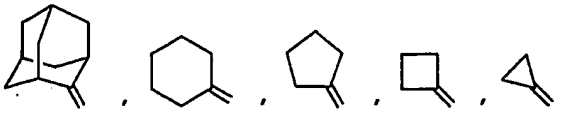
The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Therefore, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "cycloalkyl" means (C3-C10)cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like, and it is preferably cyclopentyl or cyclohexyl.

The "cycloalkylidene" is divalent cycloalkyl group.

Therefore, the partial structure:  may be exemplified

 and the like.

The "aryl" means an aromatic hydrocarbon group, such as phenyl, naphtyl, indenyl, and the like, and it is

preferably (C6-C10)aryl, more preferably phenyl.

The "aryl-(lower)alkyl" means the "(lower)alkyl" group mentioned above substituted by aryl group, and include benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, naphtylmethyl, 2-naphtylethyl, and the like, and it is preferably phenyl-(lower)alkyl, phenyl-(C1-C4)alkyl, more preferably phenyl-(C1-C2)alkyl, most preferably benzyl.

Especially, the "phenyl-(lower)alkyl" means the "(lower)alkyl" group mentioned above substituted by phenyl group, and include benzyl, 1-phenethyl, 2-phenethyl, 3-phenylpropyl, phenylisopropyl, 4-phenylbutyl, 6-phenylhexyl and the like, and it is preferably phenyl-(C1-C4)alkyl, more preferably phenyl-(C1-C2)alkyl, most preferably benzyl.

The "heteroaryl" means 5-, 6-membered or condensed polycyclic aromatic heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen, sulfur atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, or the like; 6-membered heteroaryl group such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like; and condensed polycyclic aryl group such as indolyl, isoindolyl, isoindole-1,3-dione-2-yl, quinolyl, isoquinolyl, benzofuranyl, chromenyl, benzothienyl, or the like; and is preferably 5-membered or 6-membered heteroaryl group, more preferably 5-membered or 6-membered heteroaryl group containing nitrogen atom(s), more preferably pyridinyl.

Especially, the "pyridinyl" may be 2-pyridinyl, 3-pyridinyl and 4-pyridinyl, preferably 2-pyridinyl or 3-pyridinyl. The "pyridinyl-(lower)alkyl" includes pyridinylmethyl, 1-pyridinylethyl, 2-pyridinylethyl, 3-pyridinylpropyl, pyridinylisopropyl,

4-pyridinylbutyl, 6-pyridinylhexyl and the like, and it is preferably pyridinyl-(C1-C4)alkyl, more preferably pyridinyl-(C1-C2)alkyl, most preferably pyridinylmethyl.

The "aryl-(lower)alkyl", "heteroaryl-(lower)alkyl", "aryl" and "heteroaryl" groups may respectively have 1 to 3 substituent(s) on the aryl or heteroaryl group, the number of substituent(s) is preferably 1 or 2, more preferably 1, in case that these groups has plural substituents, they may be the same or different each other, but, needless to say, these groups may not have substituent.

The "halogenated-(lower)alkyl" means the above (lower)alkyl substituted by halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, and the like, and it is preferably halogen-substituted (C1-C4)alkyl, more preferably halogen-substituted (C1-C2)alkyl, more preferably fluorine-substituted (C1-C2)alkyl, more preferably fluorine-substituted methyl, most preferably trifluoromethyl.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, and the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "aryloxy" means oxy group subsutituted with the above aryl, and includes phenyloxy, naphtyloxy, indenyloxy, and the like, and it is preferably phenyloxy.

The "halogen" may include a fluorine atom, a chlorine

atom, a bromine atom or a iodine atom, more preferably a chlorine atom.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers. However, in the portion of 2-cyanopyrrolidine, (2S) and/or (4S) isomer is more preferable.

Oxime derivatives may have two kind of geometrical isomers, that is, syn form and anti form, this invention includes both isomers.

The compounds of the formula (I) may also exist in tautomeric forms and this invention includes both mixtures and separate individual tautomers.

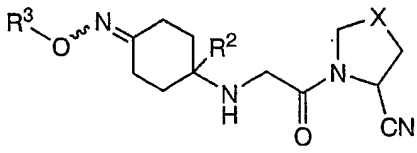
The compounds of the formula (I) and its salts may be in a form of a solvate such as hydrate, which is included within the scope of the present invention.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The compounds of this invention may be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts such as an organic acid salt (e.g., acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, or the like.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, or the like.), a salt with an amino acid (e.g., arginate, aspartate, glutamate, or the like.), or the like, and the preferable salt is hydrochloride or trifluoroacetate salt.

The compound (I) may preferably include;

a compound of the formula (II)



(II)

[wherein

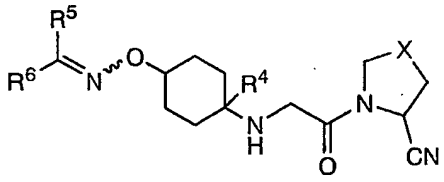
X is CFH, or CF_2,

R^2 is (lower)alkyl,

R^3 is cycloalkyl, aryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group),

the "substituent(s)" is(are) selected from the group consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy, halogen, cyano, nitro, amino and hydroxy], and

a compound of the formula (III)



(III)

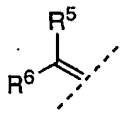
[wherein

X is CFH, or CF_2,

R^4 is (lower)alkyl,

R^5 is hydrogen, or (lower)alkyl,

R^6 is (lower)alkyl, cycloalkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), and

the partial structure:  may form cycloalkylidene,

the "substituent(s)" is(are) selected from the group

consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy, halogen, cyano, nitro, amino and hydroxy].

In the each definition of the compound formula (I) to (III), preferably,

(1) X is CFH,

(2) X is CF_2,

(3) R^2 is (C1-C4)alkyl,

(4) R^2 is (C1-C2)alkyl,

(5) R^2 is methyl,

(6) R^3 is cycloalkyl,

(7) R^3 is cyclopentyl or cyclohexyl,

(8) R^3 is benzyl (which may have 1 to 3 substituent(s) on the phenyl group),

(9) R^3 is benzyl (which may have 1 substituent on the phenyl group),

(10) R^3 is pyridinylmethyl (which may have 1 to 3 substituent(s) on the pyridinyl group),

(11) R^3 is pyridinylmethyl (which may have 1 substituent on the pyridinyl group),

(12) R^4 is (C1-C4)alkyl,

(13) R^4 is (C1-C2)alkyl,

(14) R^4 is methyl,

(15) R^5 is hydrogen,

(16) R^5 is (C1-C4)alkyl,

(17) R^5 is (C1-C2)alkyl,

(18) R^5 is methyl,

(19) R^6 is (C1-C4)alkyl,

(20) R^6 is (C1-C2)alkyl,

(21) R^6 is methyl,

(22) R^6 is phenyl (which may have 1 to 3 substituent(s)),

(23) R^6 is phenyl (which may have 1 substituent),

(24) R^6 is pyridinyl (which may have 1 to 3 substituent(s)),

(25) R^6 is pyridinyl (which may have 1 substituent),

(26) R^6 is thiazolyl (which may have 1 substituent),

(27) R^6 is thienyl (which may have 1 substituent),

(28) R^6 is pyrimidinyl (which may have 1 to 3 substituent(s)),

(29) R^6 is pyrimidinyl (which may have 1 substituent),

(30) the "substituent(s)" is(are) selected from the group consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy and halogen,

(31) the "substituent(s)" is(are) (lower)alkyl,

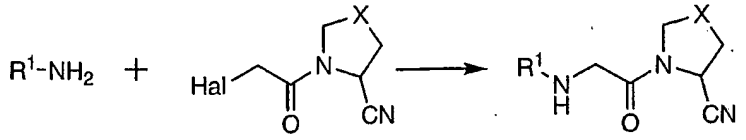
(32) the "substituent(s)" is(are) halogenated-(lower)alkyl,

(33) the "substituent(s)" is(are) aryloxy,

(34) the "substituent(s)" is(are) halogen,

The compound of the formula (I) of the present invention can be prepared according to the following Process A.

[Process A]



(IV) (V) (I)

In the above formula, R^1 and X represent the same meanings as defined above, and "Hal" represents halogen atom, especially, chlorine or bromine atom.

Process A is the process for preparing the Compound (I) from amine compound (IV) and halogenated compound (V) in solvent, preferably in the presence of base.

Compound (IV) and (V) may be purchased if it is commercial, or synthesized according to Processes C and B, respectively, mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The base employable in this process for making basic condition is not particularly limited so long as it accelerates this reaction and may include organic amine such as triethylamine, tributylamine, diisopropylethylamine;, alkali metal hydrogencarbonates such as litium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate and calcium carbonate; alkali metal hydroxides such as lithium

hydroxide, sodium hydroxide and potassium hydroxide, preferably organic amine, especially triethylamine.

To accelerate the reaction, sodium iodide may be added.

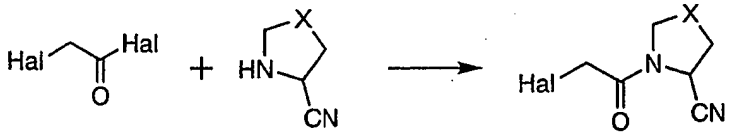
This process is generally carried out by adding the compound (V) to the solution of compound (IV). The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from -10℃ to 40℃, preferably room temperature.

The reaction time after the adding compound (V) varies depending on the starting material, the solvent, etc., but it is usually from 1hr to 24hrs, preferably from 1hr to 10hrs.

After the reaction, the mixture is quenched by aqueous solvent such as water, saturated aqueous solution of NH_4Cl, hydrochloric acid, etc, and extracted with organic solvent insoluble with water such as ethyl acetate, $CHCl_3$, etc. Preferably, the organic layer is washed with water or the like, dried over anhydrous $MgSO_4$ or Na_2SO_4, evaporated in vacuo, and the target compound (I) is purified by the conventional method such as thin layer chromatography, silica gel column chromatography, etc.

Compound (V), which is the starting compound of Process A, can be synthesized by following Process B.

[Process B]



(VI) (VII) (V)

In the above formula, X and "Hal" represent the same meanings as defined above.

Process B is the process for preparing the Compound (V) by forming amide bond in solvent in the presence of base.

Compound (VI) and (VII) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The base employable in this process is not particularly limited so long as it accelerates this process and may include organic amines such as triethylamine, tributylamine, diisopropylethylamine (DIEA), preferably DIEA.

The additive such as sodium 2-ethylhexanoate may be added to the mixture to improve the yield of this Process.

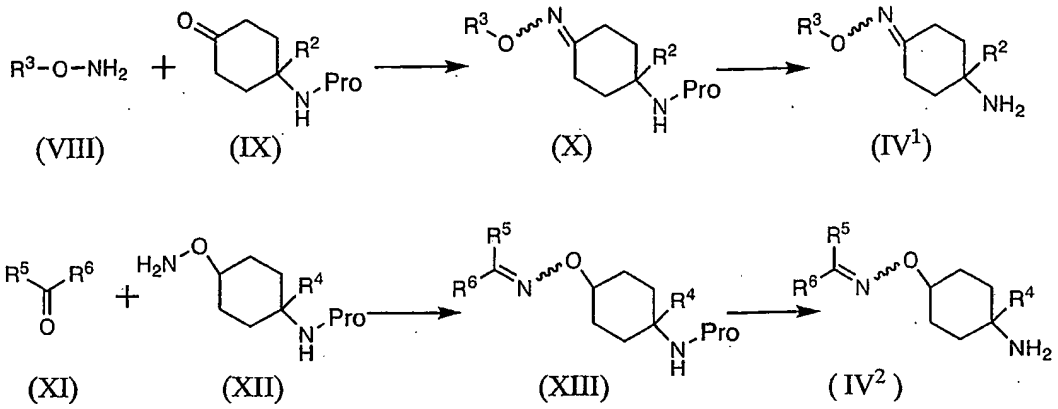
This process is generally carried out by adding the Compound (VI) to the solution of Compound (VII) and base and/or catalyst. The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from -10℃ to 30℃, preferably from 0℃ to 10℃. After the addition, the temperature is preferably raised to room temperature.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 1hrs to 24hrs.

After the reaction, the solvent is removed in vacuo, the target compound may be purified by the conventional method such as silica gel column chromatography, etc.

Compound (IV^1) and (IV^2), both of which is the starting Compound (VI) of Process A, can be synthesized by following Process C.

[Process C]



In the above formulae, R^2 to R^6 represent the same meanings as defined above, and "Pro" means the protective group of amino group.

Process C is the process for preparing the Compound (IV^1) and (IV^2) by forming oxyimino group from amino compound and carbonyl compound in solvent.

Starting Compound (VIII), (IX), (XI) and (XII) may be purchased if they are commercial, or synthesized according to general methods from commercial compounds. For example, aminooxy group of Compound (XII) can be synthesized by application of Process D described later.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, isopropanol, preferably methanol. However, in case that Compound (XI) may be used as solvent, other solvent is not necessarily needed.

This process is generally carried out by respectively adding the solution of Compound (VIII) or (XI) to the solution of Compound (IX) or (XII). The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from 10℃ to 50℃, preferably room temperature.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 1hr to 24hrs, preferably from 4hrs to 20hrs.

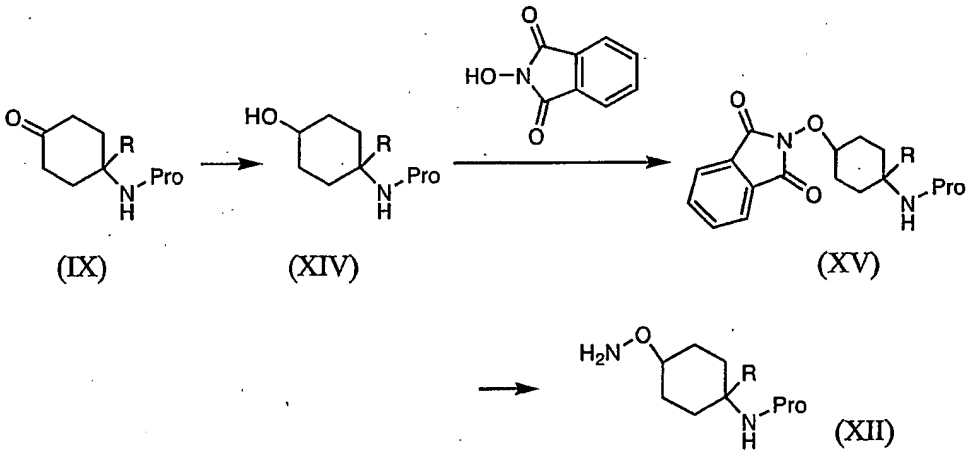
After the reaction, the solvent is removed in vacuo, and the residue is triturated with n-hexane, diisopropylether, etc. Compound (X) and (XIII) can be obtained by filtration.

In the second step (deprotecting), concerning the kind of protective group ("Pro") and cleavage reaction of the protective group, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred.

For example, when "Pro" group is carbamate group such as tert-butoxycarbonyl group, the cleavage reaction is carried out in the acidic condition in solvent by acid such as hydrochloric acid, trifluoroacetic acid, or the like. After the deprotection, excess acid and solvent are removed in vacuo, the solution of residue is washed with aqueous solvent, dried over $MgSO_4$ or Na_2SO_4, and the target compound (IV^1) and (IV^2) can be obtained by concentrating in vacuo.

The compound having aminooxy group such as Compound (XII) (the starting compound of Process C) can be synthesized by following Process D.

[Process D]



(IX) (XIV) (XV) (XII)

In the above formula, "Pro" represents the same meanings as defined above, and R represents R^2 or R^4

((lower)alkyl).

Process D is the process for preparing the compound having aminooxy group by functional group trans formation from hydroxy group.

In this process, first, Compound (IX) is reduced with ordinary method, for example reduction by H_2 gas and catalyst such as platinum oxide.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, isopropanol; acetic acid. The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from 10℃ to 50℃, preferably room temperature.

After the reaction, the target compound (XIV) can be obtained by ordinary treating.

Next, to the solution of Compound (XIV) having hydroxy group, hydroxyphthalimide and triphenylphosphine was added diisopropyl azodicarboxylate (DIAD).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from -10℃ to 50℃, preferably from 0℃ to 30℃.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 10min to 12hrs.

After the reaction, to the solution water is added, then extracted with organic solvent insoluble with water such as ethyl acetate, $CHCl_3$, etc. The organic layer is washed with aqueous solvent such as saturated aqueous solution of NaCl, dried over anhydrous $MgSO_4$ or Na_2SO_4, and evaporated in vacuo. The phthalimide derivative (XV)

can be obtained by triturating and further purification such as silica gel chromatography.

Then, phthalimide derivative (XV) was decomposed by hydrazine in solvent. That is, to the solution of phthalimide derivative, hydrazine is added.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, isopropanol, preferably ethanol.

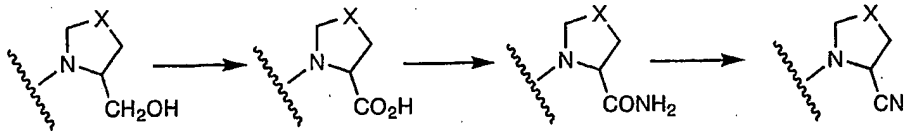
The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from 50℃ to 150℃, preferably from 70℃ to 130℃.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 10min to 6hrs.

After the reaction, the resulting precipitate is filtered off and washed with solvent, and filtrate is concentrated. Then, to the residue, aqueous solvent and organic solvent insoluble with water such as ethyl acetate are added, aqueous layer is basified and extracted. The organic layer is dried over anhydrous $MgSO_4$ or Na_2SO_4, evaporated in vacuo to obtain the target compound (XII). If necessary, further purification may be carried out.

In the above processes, functional group trans formation may timely be carried out so long as the other sites of the compounds are not affected. In the following reaction formula, the functional group trans formation of the pyrrolidine ring is shown as representative example.

[Process E]



Process E shows the representative example of

functional group trans formation. Accordingly, other reactions of functional group trans formation may be carried out.

Above processes, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method. For example of making hydrochloride or trifluoroacetate, to the compound, the solution of acid such as 4N hydrochloride/dioxane or trifluoroacetic acid is added, then the solvent and excess acid is removed and the reside is triturated appropriate solvent such as diethlether.

In the above compounds, which have reactive group, may be protected at the group on cue and be deprotected on cue. In these reactions (protecting or deprotecting steps), concerning the kind of protective group and the condition of the reaction, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being included therein.

Preparation 1-1

Methyl (2S,4R)-4-hydroxy-2-pyrrolidinecarboxylate hydrochloride

Hydroxyproline (155g) was dissolved in Hydrogen Chlororide, Methanol Reagent 10 (TCI, 900mL), and this mixture was heated at reflux for 2hrs.

The resulting mixture was cooled to room temperature, and the solvent was removed in vacuo to give the target compound as a white powder (215g).

^{1}H-NMR (in DMSO-d6) : δ 2.30-1.99(2H, m), 3.14-2.97(1H, m), 3.45-3.25(1H, m), 3.76(3H, s), 4.57-4.35(2H, m), 9.23(1H, br-s), 10.32(1H, br-s).

Preparation 1-2

1-tert-Butyl 2-methyl (2S,4R)-4-hydroxy-1,2-pyrrolidinedicarboxylate

To a solution of methyl (2S,4R)-4-hydroxy-2-pyrrolidinecarboxylate hydrochloride obtained in Preparation 1-1 (215g) in water/dioxane (800/500mL) with cooling on an ice bath, was added a solution of di-tert-butyl dicarbonate (271g)

in dioxane (150mL) and 6N NaOH (400mL) dropwise.

The reaction mixture was stirred at room temperature for 3hrs and quenched by adding with 1N HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was triturated with n-hexane to give the target compound as a white powder (200g).

^{1}H-NMR (in $CDCl_3$) : δ 1.51-1.32(9H, m), 2.39-1.82(2H, m), 3.79-3.38(5H, m), 4.58-4.31(2H, m).

Preparation 1-3

1-tert-Butyl 2-methyl (2S,4S)-4-fluoro-1,2-pyrrolidinedicarboxylate

1-tert-Butyl 2-methyl (2S,4R)-4-hydroxy-1,2-pyrrolidinedicarboxylate obtained in Preparation 1-2 (130g) and cesium fluoride (105g) was dissolved in dioxane (600mL), this mixture was cooled on an ice bath, and then a solution of diethylaminosulfur trifluoride (100g) in dioxane (20mL) was added dropwise for 30min. The reaction mixture was warmed to room temperature and stirred for 5hrs.

To the resulting mixture was added $NaHCO_3$ (400g), and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, then water (1000mL) and $CaCl_2$ (382g) in water (300mL) were added. The resulting suspension was filtered and the filtrate was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated in vacuo to give the target compound as a yellow oil (127.5g). Further purification was not attempted.

^{1}H-NMR (in $CDCl_3$) : δ 1.55-1.35(9H, m), 2.62-2.16(2H, m),

3.94-3.49(5H, m), 4.60-4.36(1H, m), 5.20(1H, br-d, J=52.8Hz).

Preparation 1-4

(2S,4S)-1-(tert-Butoxycarbonyl)-4-fluoro-2-pyrrolidinecarboxylic acid

The crude product of 1-tert-butyl 2-methyl (2S,4S)-4-fluoro-1,2-pyrrolidinedicarboxylate obtained in Preparation 1-3 (127.5g) was dissolved in methanol (400mL) and then 1N NaOH (800mL) was added at room temperature.

After stirring for 1.5hrs, the resulting mixture was washed with diethyl ether, acidified with 1N HCl (1000mL), and then was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was triturated with ethyl acetate to give the target compound as a white powder (64g).

^{1}H-NMR (in $CDCl_3$) : δ 1.62-1.31(9H, m), 2.94-2.09(2H, m), 4.01-3.44(2H, m), 4.66-4.37(1H, m), 5.22(1H, br-d, J=51.9Hz).

Preparation 1-5

tert-Butyl (2S,4S)-2-aminocarbonyl-4-fluoro-1-pyrrolidinecarboxylate

To a mixture of (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoro-2-pyrrolidinecarboxylic acid obtained in Preparation 1-4 (66g), 1-hydroxybenzotriazole hydrate (45g) in acetonitrile (1500mL) with cooling on an ice bath, was added WSC·HCl (water soluble carbodiimide hydrochloride, 82g). After the mixture was stirred for 45min, 28% aqueous NH_3

(43mL) was added at the same temperature. The resulting mixture was warmed to room temperature and stirred for 15min.

The reaction mixture was filtered and the filtration was evaporated in vacuo. After dilution with ethyl acetate, the reaction mixture was washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and filtered. After removal the solvent, the target compound was obtained as a white powder (46g).

^{1}H-NMR (in $CDCl_3$) : δ 1.58-1.36(9H, m), 2.99-2.02(2H, m), 3.99-3.43(2H, m), 4.57-4.23(1H, m), 5.23(1H, br-d, J=51.6Hz), 5.69-5.40(1H, m), 6.79-6.05(1H, m).
MS : 233.10 (ES+).

Preparation 1-6
(2S,4S)-4-Fluoro-2-pyrrolidinecarboxamide hydrochloride

tert-Butyl (2S,4S)-2-aminocarbonyl-4-fluoro-1-pyrrolidinecarboxylate obtained in Preparation 1-5 (46g) was dissolved in 4N HCl in dioxane (200mL) and the resulting mixture was stirred for 10min at room temperature.

After removal of the solvent, the resulting residue was triturated with ethyl acetate to give the target compound as a white powder (34g).

^{1}H-NMR (in DMSO-d6) : δ 2.84-2.00(2H, m), 4.10-3.09(2H, m), 4.44-4.15(1H, m), 5.39(1H, br-d, J=52.5Hz), 7.73(1H, br-s), 8.09(1H, br-s), 8.76(1H, br-s), 10.62(1H, br-s).
MS : 132.94 (ES+).

Preparation 1-7
(2S,4S)-1-Chloroacetyl-4-fluoro-2-pyrrolidinecarboxamide

To a mixture of (2S,4S)-4-fluoro-2-pyrrolidinecarboxamide hydrochloride obtained in Preparation 1-6 (33g) and sodium 2-ethylhexanoate (70g) in tetrahydrofuran (500mL) with cooling on an ice bath, was added chloroacethyl chloride (24.3g).

After stirring for 2hrs, the resulting residue was then poured onto buchner funnel/filter paper and washed with ethyl acetate. The solvent was removed in vacuo and the resulting residue was triturated with diethylether to give the target compound (34g) as a white powder.

^{1}H-NMR (in $CDCl_3$) : δ 2.58-2.03(1H, m), 3.05-2.58(1H, m), 4.17-3.68(4H, m), 4.85-4.54(1H, m), 5.36(1H, br-d, J=52.5Hz), 5.88-5.49(1H, m), 6.63-6.19(1H, m).

Preparation 1-8

(2S,4S)-1-Chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile

To a solution of (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarboxamide obtained in Preparation 1-7 (34g) in tetrahydrofuran (800m), was added trifluoroacetic anhydride (28mL) at room temperature.

After stirring for 15min, the resulting mixture was concentrated in vacuo. The resulting residue was triturated with ethyl acetate to give the target compound (22g) as a white powder.

^{1}H-NMR (in $CDCl_3$) : δ 2.52-2.22(1H, m), 2.87-2.59(1H, m), 4.33-3.75(4H, m), 5.12-4.87(1H, m), 5.41(1H, br-d, J=50.7Hz).

Preparation 2-1

Ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate

To a solution of ethyl 4-oxocyclohexanecarboxylate (100g) in toluene (500mL), were added ethylene glycol (36mL) and a catalytic amount of p-toluenesulfonic acid, and the resulting mixture was refluxed azeotropically for 2hrs.

Then the solution was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, and dried over $MgSO_4$. After removal of the solvent, the target compound was obtained (130g) as a pale yellow oil.

^{1}H-NMR (in $CDCl_3$) : δ 1.18(3H, t, J=6.9Hz), 1.68-1.48(2H, m), 2.01-1.70(6H, m), 2.40-2.25(1H, m), 3.94(4H, s), 4.13(2H, q, J=6.9Hz).

MS : 250.09 (ES+).

Preparation 2-2

Ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

To a solution of diisopropylamine (70mL) in tetrahydrofuran (500mL), was added n-butyllithium (1.6M, 300mL) at -40℃ dropwise for 25min and the reaction mixture was warmed to -10℃, then cooled to -65℃. To this solution was added a solution of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate obtained in Preparation 2-1 in tetrahydrofuran (100mL) dropwise at the same temperature. The reaction mixture was stirred at -50℃ for 1hr, and then methyl iodide (31mL) was added. The reaction mixture was stirred at between -40 and -30℃ for 0.5hr, then warmed to -10℃.

The solution was poured into saturated aqueous NaCl

solution and ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, and dried over $MgSO_4$. After removal of the solvent, the target compound was obtained as a yellow oil (70g).

Preparation 2-3
8-Methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid

Ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate obtained in Preparation 2-2 (70g) was dissolved in 3N NaOH (500mL)-methanol (400mL), and the reaction mixture was heated at reflux for 0.5hr, and then was cooled to room temperature.

After removal of the organic solvent in vacuo, the aqueous solution was neutralized with 3N HCl and 10% aqueous citric acid to pH5. The solution was saponificated with NaCl, and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo, the resulting residue was triturated with diisopropylether to give the target compound (46g) as a white powder.

^{1}H-NMR (in $CDCl_3$) : δ 1.26(3H, s), 1.62-1.45(2H, m), 1.72-1.62(4H, m), 2.19-2.08(2H, m), 3.94(4H, s).
MS : 199.78 (ES-).

Preparation 2-4
tert-Butyl 8-methyl-1,4-dioxaspiro[4.5]dec-8-ylcarbamate

To a solution of 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid obtained in Preparation 2-3 (45g) in toluene (450mL), were added diphenylphosphoryl azide (53mL) and triethylamine (35mL), and the reaction mixture was heated at 100℃ for

1hr. The resulting mixture was cooled on an ice bath, washed with saturated aqueous $NaHCO_3$ solution, water and saturated aqueous NaCl solution, and dried over $MgSO_4$.

After removal of the solvent in vacuo, the isocyanate intermediate was obtained as a pale yellow oil. This oil was dissolved in dimethylacetamide (270mL), and to this solution was added potassium tert-butoxide (26g) as portions with cooling on an ice bath. After stirring for 1hr, the reaction mixture was poured into ice-water (300mL). The resulting precipitate was collected, washed with water (100mL) to give the target compound (53g) as a white powder.

^{1}H-NMR (in $CDCl_3$) : δ 1.33(3H, s), 1.43(9H, s), 1.76-1.53(6H, m), 2.11-1.95(2H, m), 3.94(4H, s), 4.39(1H, br-s).

Preparation 2-5

tert-Butyl 1-methyl-4-oxocyclohexylcarbamate

tert-Butyl 8-methyl-1,4-dioxaspiro[4.5]dec-8-ylcarbamate obtained in Preaparation 2-4 (53g) was dissolved in tetrahydrofuran (300mL) and p-toluenesulfonic acid (74g) in water (300mL) at room temperature, and the reaction mixture was stirred at the same temperature for 16hrs.

The resulting solution was neutralized with $NaHCO_3$, and extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. After removal of the solvent, the residue was triturated with n-hexane to give the target compound (26g) as a white powder.

^{1}H-NMR (in $CDCl_3$) : δ 1.43(3H, s), 1.46(9H, s), 1.87-1.69(2H, m), 2.54-2.21(6H, m), 4.50(1H, br-s).

Example 1-1
tert-Butyl 4-hydroxy-1-methylcyclohexylcarbamate

To a solution of tert-butyl 1-methyl-4-oxocyclohexylcarbamate obtained in Preparation 2-5 (128g) dissolved in acetic acid (1000mL), was added platinum oxide (6.4g). The reaction mixture was hydrogenated under H_2 2.0atm at room temperature for 8hrs.

The resulting mixture was filtered, and the solvent was removed in vacuo. The residue was dissolved in saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo, the residue was triturated with ethyl acetate to give the target compound (128g, cis/trans=12:1) as a colorless oil.

^{1}H-NMR (in $CDCl_3$) (cis) : δ 1.89-1.18(18H, m), 2.17-2.05(2H, m), 3.70-3.55(1H, m), 4.36(1H, br-s).

Example 1-2
tert-Butyl 4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]-1-methylcyclohexylcarbamate

To a solution of tert-butyl 4-hydroxy-1-methylcyclohexylcarbamate obtained in Example 1-1 (75g), hydroxyphthalimide (54g) and triphenylphosphine (86g) in tetrahydrofuran (750mL) with cooling on an ice bath, was added diisopropyl azodicarboxylate (64mL) dropwise for 20min, and the reaction mixture was stirred at the same temperature for 20min.

The reaction mixture was quenched by pouring water.

The organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo, the residue was triturated with diethylether, and this precipitate was filtered off. After removal of the solvent, the resulting residue was purified with silica gel chromatography (n-hexane:ethyl acetate=4:1) to give the target compound as a white powder (84g).

^{1}H-NMR (in $CDCl_3$) : δ 2.03-1.17(20H, m), 4.41-4.30(1H, m), 7.77-7.72(2H, m), 7.86-7.80(2H, m).

Example 1-3

tert-Butyl 4-aminooxy-1-methylcyclohexylcarbamate

tert-Butyl 4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]-1-methylcyclohexylcarbamate obtained in Example 1-2 (84g) was dissolved in ethanol (840mL). This solution was warmed to 80℃ and $NH_2NH_2 \cdot H_2O$ was added at the same temperature. The resulting mixture was heated at reflux for 30min, and then was cooled on an ice bath. The resulting precipitate was filtered off, washed with ethanol, and the filtrate was concentrated in vacuo.

The resulting mixture was diluted with water and acidified with concentrated HCl. The aqueous layer was washed with ethyl acetate, basified with NaOH, saturated with NaCl, and was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo, the target compound was given as a yellow oil (16g).

^{1}H-NMR (in $CDCl_3$) : δ 1.31(3H, s), 1.43(9H, s), 1.84-1.53(8H, m), 3.69-3.55(1H, m), 4.38(1H, br-s), 5.24(1H, br-s).

Example 1-4
tert-Butyl 1-methyl-4-({[(1E)-3-pyridinylmethylidene]amino}oxy)cyclohexylcarbamate

To a cold stirred solution(-78℃) of tert-butyl 4-(aminooxy)-1-methylcyclohexylcarbamate obtained in Example 1-3 (16.0g) in methanol (160mL), was added nicotinaldehyde (6.18mL). The mixture was stirred at room temperature for 16hrs.

The solution was concentrated in vacuo. The residue was triturated with n-hexane, then filtered to provide the target compound (17.1g) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.45(9H, s), 1.53-1.95(8H, m), 4.33(1H, br-s), 4.40(1H, br-s), 7.31(1H, dd, J=4.9, 8.0Hz), 7.96(1H, dt, J=1.8, 8.0Hz), 8.11(1H, s), 8.59(1H, dd, J=1.8, 4.9Hz), 8.74(1H, d, J=1.8Hz).

Example 1-5
Nicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

Trifluoroacetic acid (100mL) was added to a solution of 1-methyl-4-({[(1E)-3-pyridinylmethylidene]amino}-oxy)cyclohexylcarbamate obtained in Example 1-4 (11.0g) in tetrahydrofuran (50mL) with cooling on an ice bath. The reaction mixture was stirred at room temperature for 1hr.

The mixture was concentrated in vacuo. The residue was used in the next step without purification (28.4g).

^{1}H-NMR (300MHz, DMSO) : δ 1.30(3H, s), 1.56-1.83(6H, m), 1.90-2.09(2H, m), 4.20(1H, m), 7.52(1H, dd, J=4.8, 7.9Hz), 7.90(2H, br-s), 8.09(1H, d, J=7.9Hz), 8.33(1H, s), 8.65(1H,

br-s), 8.82(1H, br-s).

Example 1-6

(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-3-pyridinylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

To a stirred solution of nicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 1-5 (28.4g) in dimethylformamide (130mL), were added K_2CO_3 (24.2g), (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 (5.73g), and sodium iodide (50mg).

The mixture was stirred for 2hrs at 50℃ and quenched by adding water (200mL). The aqueous layer was neutralized with 1N HCl and extracted with ethyl acetate. The combined organic layers were extracted with 0.5N HCl. The aqueous layer was separated and basified with $NaHCO_3$, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried and concentrated in vacuo. The residue was purified by silica gel column chromatography (chloroform/methanol=5:1). The residue was crystallized from ethanol to provide the target compound (7.2g) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.15(3×1/5H, s), 1.38-1.53(2H, m), 1.57-1.79(4H, m), 1.97(2H, br-s), 2.20-2.58(1H, m), 2.70(1×4/5H, t, J=15.7Hz), 2.77(1×1/5H, t, J=15.7Hz), 3.30-4.10(4H, m), 4.23-4.35(1H, m), 4.97(1×4/5H, d, J=8.9 Hz), 5.11(1×1/5H, d, J=8.9Hz), 5.36(1 × 1/5H, br-d, J=51.2Hz), 5.45(1 × 4/5H, br-d, J=51.2Hz), 7.30(1H, dd, J=4.9, 7.8Hz), 7.97(1H, dt, J=2.0, 7.8Hz), 8.10(1H, s), 8.59(1H, dd, J=2.0, 4.9Hz), 8.73(1H,

d, J=2.0Hz).
MS (ES+) : m/e 388.18.

Example 2-1
2-(2-Pyridinylmethoxy)-1H-isoindole-1,3(2H)-dione

To a solution of 2-pyridinylmethanol (50g), 2-hydroxy-1H-isoindole-1,3(2H)-dione (75g) and triphenylphosphine (144g) in tetrahydrofuran (500mL) at room temperature, was added diisopropyl azodicarboxylate (100mL) and stirred for 15min at the same temperature.

The reaction precipitate was filtered off and washed with tetrahydrofuran to give the target compound (60g) as a white powder.

^{1}H-NMR (in $CDCl_3$) : δ 5.34(s, 2H), 7.30-7.26(m, 1H), 7.83-7.72(m, 6H), 8.56-8.55(m, 1H).

Example 2-2
O-(2-Pyridinylmethyl)hydroxylamine

2-(2-Pyridinylmethoxy)-1H-isoindole-1,3(2H)-dione obtained in Example 2-1 (60g) was dissolved in ethanol (1000mL). This solution was warmed to 80℃ and $NH_2NH_2 \cdot H_2O$ was added at the same temperature. The resulting mixture was heated at reflux for 30min and then was cooled to room temperature.

The resulting precipitate was filtered off, washed with ethyl acetate, and the filtrate was concentrated in vacuo. The resulting mixture was diluted with water and acidified with concentrated HCl. The aqueous layer was washed with ethyl acetate, basified with NaOH, saturated with NaCl, and was extracted three times with chloroform. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered. After removal of the solvent

in vacuo, the target compound was given as a yellow oil (20g).

^{1}H-NMR (in $CDCl_3$) : δ 4.84(s, 2H), 5.63(br-s, 2H), 7.26-7.16(m, 1H), 7.43-7.34(m, 1H), 7.77-7.65(m, 1H), 8.66-8.52(m, 1H).

Example 2-3

tert-Butyl 1-methyl-4-[(2-pyridinylmethoxy)imino]cyclohexylcarbamate

The title compound (1.24g) was prepared from tert-butyl 1-methyl-4-oxocyclohexylcarbamate obtained in Preparation 2-5 and O-(2-pyridinylmethyl)hydroxylamine obtained in Example 2-2 in a similar manner to that of Example 3-3 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36(3H, s), 1.44(9H, s), 1.46-1.65(2H, m), 2.06-2.32(5H, m), 2.98(1H, dt, J=4.8, 15.0Hz), 4.40(1H, br-s), 5.19(2H, s), 7.18(1H, br-dd, J=4.8, 7.6Hz), 7.35 1H, d, J=7.6Hz), 7.68(1H, dt, J=1.8, 7.6Hz), 8.57(1H, br-d, J=4.8Hz).
MS (ES+) : m/e 334.24.

Example 2-4

4-Amino-4-methylcyclohexanone O-(2-pyridinylmethyl)oxime

The title compound (918mg) was prepared from tert-butyl 1-methyl-4-[(2-pyridinylmethoxy)imino]-cyclohexylcarbamate obtained in Example 2-3 in a similar manner to that of Example 3-4 described later.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.20(3H, s), 1.47(2H, br-s),

1.54-1.70(4H, m), 2.24(1H, dt, J=6.0, 15.2Hz), 2.36-2.46(1H, m), 2.54-2.64(1H, m), 2.74(1H, dt, J=6.0, 15.4Hz), 5.20(2H, s), 7.18(1H, br-dt, J=4.8, 7.6Hz), 7.39(1H, d, J=7.6Hz), 7.68(1H, dt, J=1.8, 7.6Hz), 8.57(1H, ddd, J=0.9, 1.8, 4.8Hz)
MS (ES+) : m/e 234.20.

Example 2-5
4-Fluoro-1-[({1-methyl-4-[(2-pyridinylmethoxy)imino]cyclohexyl}amino)acetyl]-2-pyrrolidinecarbonitrile dihydrochloride

The title compound (69.49g) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 4-amino-4-methylcyclohexanone O-(2-pyridinylmethyl)-oxime obtained in Example 2-4 in a similar manner to that of Example 3-5 described later.

^{1}H-NMR (300MHz, $CDCl_3$, free-form) : δ 1.14(3×4/5H, s), 1.17(3×1/5H, s), 1.45-2.03(5H, m), 2.17-2.88(5H, m), 3.30-4.20(4H, m), 4.97 (1H, d, J=9.5Hz), 5.19(2H, s), 5.37(1 × 1/5H, br-d, J=51.5Hz), 5.45(1 × 4/5H, br-d, J=51.5Hz), 7.19(1H, br-dd, J=5.0, 7.7Hz), 7.35(1H, d, J=7.7Hz), 7.69(1H, dt, J=1.8, 7.7Hz), 8.57(1H, br-d, J=5.0Hz).
MS (ES+) : m/e 388.12 (free-form).

Example 3-1
2-(3-Pyridinylmethoxy)-1H-isoindole-1,3(2H)-dione

The title compound (5.77g) was prepared from 3-pyridinylmethanol in a similar manner to that of Example 2-1.

Example 3-2
3-[(Aminooxy)methyl]pyridine

The title compound (1.50g) was prepared from 2-(3-pyridinylmethoxy)-1H-isoindole-1,3(2H)-dione obtained in Example 3-1 in a similar manner to that of Example 2-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 4.71(2H, s), 5.47(2H, br-s), 7.30(1H, dd, J=4.9, 7.7Hz), 7.70(1H, dt, J=1.7, 7.7Hz), 8.57(1H, dd, J=1.7, 4.9Hz), 8.62(1H, d, J=1.7Hz)
MS (ES+) : m/e 124.93.

Example 3-3
tert-Butyl 1-methyl-4-[(3-pyridinylmethoxy)imino]cyclohexylcarbamate

To a stirred solution of tert-butyl 1-methyl-4-oxocyclohexylcarbamate obtained in Preparation 2-5 (1.00g) in methanol (0.5mL), was added 3-[(aminooxy)methyl]pyridine obtained in Example 3-2 (552mg). The mixture was stirred for 5hrs.

The solution was concentrated in vacuo. The residue was triturated with diisopropylether, then filtrated to provide the target compound (892mg) as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.44(9H, s), 1.45-1.60(2H, m), 2.05-2.29(5H, m), 2.81-2.93(1H, m), 4.40(1H, br-s), 5.06(2H, s), 7.27(1H, dd, J=4.8, 7.9Hz), 7.67(1H, d, J=1.7, 7.9Hz), 8.54(1H, dd, J=1.7, 5.0Hz), 8.60(1H, br-d, J=1.7Hz).
MS (ES+) : m/e 334.20.

Example 3-4
4-Amino-4-methylcyclohexanone O-(3-pyridinylmethyl)ox

ime

To a cold stirred solution of tert-butyl 1-methyl-4-[(3-pyridinylmethoxy)imino]cyclohexylcarbamate obtained in Example 3-3 (250mg) in methanol (0.5mL), was added 4N HCl solution in dioxane (1.5mL).

The mixture was stirred for 2hrs, and concentrated in vacuo. The residue was acidified with 1N HCl, rinsed with ethyl acetate. The aqueous layer was alkalized with saturated aqueous $NaHCO_3$ solution, then extracted with chloroform. The combined organic layer was dried and filtrated. The filtrate was concentrated in vacuo to provide the target compound (117mg) as an oil.

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.19(3H, s), 1.50-1.63(3H, m), 1.77-1.83(1H, m), 2.16-2.71(4H, m), 5.07(2H, s), 7.27(1H, ddd, J=0.6, 4.8, 7.7Hz), 7.67(1H, dddd, J=0.6, 1.7, 2.0, 7.7Hz), 8.54(1H, dd, J=1.7, 4.8Hz), 8.61(1H, dd, J=0.6, 2.0Hz).
MS (ES+) : m/e 234.13.

Example 3-5
(2S,4S)-4-Fluoro-1-[({1-methyl-4-[(3-pyridinylmethoxy)imino]cyclohexyl}amino)acetyl]-2-pyrrolidinecarbonitrile dihydrochloride

To a stirred solution of 4-amino-4-methylcyclohexanone O-(3-pyridinylmethyl)-oxime obtained in Example 3-4 (110mg) in tetrahydrofuran (2mL), were added triethylamine (0.066mL), (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 (75.0mg), and sodium iodide (7mg).

The mixture was stirred for 6hrs and diluted with water. The aqueous layer was extracted with ethyl acetate.

The combined organic layers were washed with saturated aqueous NaCl solution, dried and filtered. After removal of the solvent in vacuo, the residue was purified by preparative thin layer chromatography (chloroform/methanol=5:1). The provided oil was dissolved in ethyl acetate and 4N HCl-dioxane was added, then the precipitated was collected by filtration under N_2 to provide the target compound (66.5mg) as a white solid.

^{1}H-NMR (300MHz, DMSO) : δ 1.42(3H, s), 1.73-2.00(3H, m), 2.03-2.57(6H, m), 3.10(1H, br-d, J=11.5Hz), 3.70-4.30(4H, m), 5.08(1H, d, J=7.9Hz), 5.19(2H, s), 5.57(1H, br-d, J=52.6Hz), 7.87(1H, br-s), 8.28(1H, br-s), 8.77(1H, s), 8.79(1H, s), 9.05(1H, br-s), 9.17(1H, br-s).
MS (ES+) : m/e 388.16.

Example 4-1
2-[(6-Methyl-2-pyridinyl)methoxy]-1H-isoindole-1,3(2H)-dione

The title compound (4.52g) was prepared from (6-methyl-2-pyridinyl)methanol in a similar manner to that of Example 2-1.

Example 4-2
2-[(Aminooxy)methyl]-6-methylpyridine

The title compound (1.16g) was prepared from 2-[(6-methyl-2-pyridinyl)methoxy]-1H-isoindole-1,3(2H)-dione obtained in Example 4-1 in a similar manner to that of Example 2-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.57(3H, s), 4.80(2H, s), 5.61(2H, br-s), 7.08(1H, d, J=7.7Hz), 7.18(1H, d, J=7.7Hz), 7.59(1H, t, J=7.7Hz).

MS (ES+) : m/e 139.01.

Example 4-3

tert-Butyl 1-methyl-4-{[(6-methyl-2-pyridinyl)methoxy]imino}cyclohexylcarbamate

The title compound (260mg) was prepared from tert-butyl 1-methyl-4-oxocyclohexylcarbamate obtained in Preparation 2-5 and 2-[(aminooxy)methyl]-6-methylpyridine obtained in Example 4-2 in a similar manner to that of Example 3-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36(3H, s), 1.44(9H, s), 1.5-1.6(2H, m), 2.1-2.3(5H, m), 2.55(3H, s), 2.97(1H, dt, J=4.7, 15.2Hz), 4.41(1H, br-s), 5.15(2H, s), 7.04(1H, d, J=7.8Hz), 7.14(1H, d, J=7.8Hz), 7.56(1H, t, J=7.8Hz)
MS (ES+) : m/e 384.24.

Example 4-4

4-Amino-4-methylcyclohexanone O-[(6-methyl-2-pyridinyl)methyl]oxime

The title compound (143mg) was prepared from tert-butyl 1-methyl-4-{[(6-methyl-2-pyridinyl)-methoxy]imino}cyclohexylcarbamate obtained in Example 4-3 in a similar manner to that of Example 3-4.

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.22(3H, s), 1.55-1.70(3H, m), 2.24(1H, dt, J=5.8, 14.5Hz), 2.41(1H, ddd, J=6.2, 8.1, 14.7Hz), 2.55(3H, s), 2.59(1H, dd, J=6.6, 14.7Hz), 2.61(1H, dd, J=6.2, 11.5Hz), 2.74(1H, dt, J=6.2, 15.1Hz), 5.16(2H, s), 7.04(1H, d, J=7.7Hz), 7.15(1H, d, J=7.7Hz), 7.57(1H, t, J=7.7Hz).
MS (ES+) : m/e 248.18.

Example 4-5
(2S,4S)-4-Fluoro-1-{[(1-methyl-4-{[(6-methyl-2-pyridinyl)methoxy]imino}cyclohexyl)amino]acetyl}-2-pyrrolidinecarbonitrile dihydrochloride

The title compound (95.2mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 4-amino-4-methylcyclohexanone O-[(6-methyl-2-pyridinyl)methyl]oxime obtained in Example 4-4 in a similar manner to that of Example 3-5.

^{1}H-NMR (300MHz, DMSO) : δ 1.43(3H, s), 1.80-2.10(3H, m), 2.17-2.55(6H, m), 2.74(3H, s), 3.15(1H, br-d, J=14.7Hz), 3.70-4.27(4H, m), 5.08(1H, br-d, J=8.1Hz), 5.36(2H, s), 5.57(1H, br-d, J=52.0Hz), 7.68(1H, d, J=8.0Hz), 7.75(1H, d, J=8.0Hz), 8.35(1H, t, J=8.0Hz), 9.12(1H, br-s), 9.36(1H, br-s).
MS (ES+) : m/e 402.18.

Example 5-1
2-[(2-Methyl-3-pyridinyl)methoxy]-1H-isoindole-1,3(2H)-dione

The title compound (1.8g) was prepared from (2-methyl-3-pyridinyl)methanol in a similar manner to that of Example 2-1.

Example 5-2
3-[(Aminooxy)methyl]-2-methylpyridine

The title compound (676mg) was prepared from 2-[(2-methyl-3-pyridinyl)methoxy]-1H-isoindole-1,3(2H)-dione obtained in Example 5-1 in a similar manner to that of Example 2-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.58(3H, s), 4.72(2H, s), 5.48(2H, br-s), 7.13(1H, dd, J=4.9, 7.7Hz), 7.61(1H, dd, J=1.8, 7.7Hz), 8.45(1H, dd, J=1.8, 4.9Hz).
MS (ES+) : m/e 123.96.

Example 5-3
tert-Butyl 1-methyl-4-{[(2-methyl-3-pyridinyl)methoxy]imino}cyclohexylcarbamate

The title compound (314mg) was prepared from tert-butyl 1-methyl-4-oxocyclohexylcarbamate obtained in Preparation 2-5 and 3-[(aminooxy)methyl]-2-methylpyridine by Example 5-2 in a similar manner to that of Example 3-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.44(9H, s), 1.45-1.62(2H, m), 2.06-2.30(5H, m), 2.56(3H, s), 2.82-94(1H, m), 4.34(1H, br-s), 5.06(2H, s), 7.12(1H, dd, J=4.8, 7.7Hz), 7.59(1H, dd, J=1.8, 7.7Hz), 8.43(1H, dd, J=1.8, 4.9Hz).
MS (ES+) : m/e 348.24.

Example 5-4
4-Amino-4-methylcyclohexanone O-[(2-methyl-3-pyridinyl)methyl]oxime

The title compound (155.1mg) was prepared from tert-butyl 1-methyl-4-{[(2-methyl-3-pyridinyl)-methoxy]imino}cyclohexylcarbamate obtained in Example 5-3 in a similar manner to that of Example 3-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.21(3H, s), 1.54-1.65(4H, m), 1.80(2H, br-s), 2.23(1H, dt, J=5.9, 14.7Hz), 2.34-2.71(3H, m), 2.56(3H, s), 5.07(2H, s), 7.12(1H, dd, J=5.0, 7.5Hz),

7.59(1H, dd, J=1.5, 7.5Hz), 8.43(1H, dd, J=1.5, 5.0Hz).
MS (ES+) : m/e 248.19.

Example 5-5

(2S,4S)-4-Fluoro-1-{[(1-methyl-4-{[(2-methyl-3-pyridinyl)methoxy]imino}cyclohexyl)amino]acetyl}-2-pyrrolidinecarbonitrile dihydrochloride

The title compound (179mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 4-amino-4-methylcyclohexanone O-[(2-methyl-3-pyridinyl)methyl]oxime obtained in Example 5-4 in a similar manner to that of Example 3-5.

^{1}H-NMR (300MHz, DMSO) : δ 1.42(3H, s), 1.70-1.99(3H, m), 2.05-2.50(6H, m), 2.71(3H, s), 3.10(1H, br-d, J=16.1Hz), 3.65-4.30(4H, m), 5.08(1H, d, J=8.1Hz), 5.20(2H, s), 5.61(1H, br-d, J=52.6Hz), 7.80(1H, br-s), 8.23-8.32(1H, m), 8.67(1H, br-d, J=5.1Hz), 9.07(1H, br-s), 9.18(1H, br-s).
MS (ES+) : m/e 402.17.

Example 6-1

2-[(6-Chloro-3-pyridinyl)methoxy]-1H-isoindole-1,3(2H)-dione

The title compound (1.65g) was prepared from (6-chloro-3-pyridinyl)methanol in a similar manner to that of Example 2-1.

Example 6-2

5-[(Aminooxy)methyl]-2-chloropyridine

The title compound (40mg) was prepared from

2-[(6-chloro-3-pyridinyl)methoxy]-1H-isoindole-1,3(2H)-dione obtained in Example 6-1 in a similar manner to that of Example 2-2.

^{1}H-NMR (300MHz, DMSO) : δ 5.11(2H, s), 7.61(1H, d, J=8.0Hz), 7.95(1H, dd, J=2.4, 8.0Hz), 8.40(1H, d, J=2.4Hz), 10.9(2H, br-s).
MS (ES-) : m/e 158.92.

Example 6-3
tert-Butyl 4-{[(6-chloro-3-pyridinyl)methoxy]imino}-1-methylcyclohexylcarbamate

The title compound (252mg) was prepared from tert-butyl 1-methyl-4-oxocyclohexylcarbamate obtained in Preparation 2-5 and 5-[(aminooxy)methyl]-2-chloropyridine by Example 6-2 in a similar manner to that of Example 3-3.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.44(9H, s), 1.40-1.65(2H, m), 2.08-2.50(5H, m), 2.80-2.90(1H, m), 4.38(1H, br-s), 5.02(2H, s), 7.32(1H, d, J=8.1Hz), 7.64(1H, dd, J=2.4, 8.1Hz), 8.36(1H, d, J=2.4Hz).
MS (ES+) : m/e 368.12.

Example 6-4
4-Amino-4-methylcyclohexanone O-[(6-chloro-3-pyridinyl)methyl]oxime

The title compound (174mg) was prepared from tert-butyl 4-{[(6-chloro-3-pyridinyl)methoxy]imino}-1-methylcyclohexylcarbamate obtained in Example 6-3 in a similar manner to that of Example 3-4.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.18(3H, s), 1.49-1.62(4H, m),

2.20(1H, dt, J=5.9, 14.8Hz), 2.33-2.54(2H, m), 2.65(1H, dt, J=5.9, 14.8Hz), 5.03(2H, s), 7.31(1H, d, J=8.1Hz), 7.64(1H, dd, J=2.4, 8.1Hz), 8.36(1H, d, J=2.4Hz).
MS (ES+) : m/e 268.15.

Example 6-5
(2S,4S)-1-{[(4-{[(6-Chloro-3-pyridinyl)methoxy]imino}-1-methylcyclohexyl)amino]acetyl}-4-fluoro-2-pyrrolidinecarbonitrile

The title compound (151mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 4-amino-4-methylcyclohexanone O-[(6-chloro-3-pyridinyl)methyl]oxime obtained in Example 6-4 in a similar manner to that of Example 3-5.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.11(3×3/4H, s), 1.14(3×1/4H, s), 1.40-1.69(4H, m), 2.10-2.47(4H, m), 2.62-2.80(2H, m), 3.28-4.00(4H, m), 4.96(1H, d, J=9.5Hz), 5.03(2H, s), 5.36(1 × 1/4H, br-d, J=51.3Hz), 5.44(1 × 3/4H, br-d, J=51.3Hz), 7.31(1H, d, J=8.2Hz), 7.64(1H, dd, J=2.2. 8.2Hz), 8.36(1H, d, J=2.2Hz).
MS (ES+) : m/e 422.11.

Example 7-1
2-Pyridinecarbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

To a solution of tert-butyl trans-1-methyl-4-({[(1E)-2-pyridinylmethylene]amino}oxy)cyclohexyl]carbamate (436mg) in tetrahydrofuran (1.5mL), was added trifluoroacetic acid (3mL) in an ice-water bath. The reaction mixture was stirred at room temperature for 1.5hrs. The mixture was concentrated in

vacuo. The residue was used in the next step without purification (1.09g).

Example 7-2

(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-2-pyridinylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

To a stirred solution of 2-pyridinecarbaldehyde O-(trans-4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) in dimethylformamide (2mL), were added K_2CO_3 (935mg), (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 (237mg) and sodium iodide (9mg).

The mixture was stirred for 4hrs at 50℃ and diluted with water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried and concentrated in vacuo. The residue was crystallized from ethanol to provide the target compound as a white solid (150mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.15(3×1/5H, s), 1.39-1.52(2H, m), 1.55-1.80(4H, m), 1.90-2.05(2H, m), 2.20-2.56(1H, m), 2.67(1×4/5H, t, J=15.0Hz), 2.77(1×1/5H, t, J=14.9Hz), 3.30-4.10(4H, m), 4.32(1H, br-s), 4.71(1×4/5H, d, J=9.2Hz), 5.11(1×1/5H, d, J=8.8Hz), 5.36(1×1/5H, br-d, J=52.2Hz), 5.43(1×4/5H, br-t, J=3.5, 50.9Hz), 7.25(1H, m), 7.69(1H, dt, J=1.8, 7.9Hz), 7.80(1H, dt, J=0.9, 7.9Hz), 8.18(1H, s), 8.61(1H, ddd, J=0.9, 1.8, 5.0Hz).

MS (ES+) : m/e 388.14.

Example 8-1

1-tert-Butyl 2-methyl (2S)-4-oxo-1,2-pyrrolidinedicarboxylate

To a solution of oxalyl chloride in dichloromethane (50mL) at -70℃, was added dimethylsulfoxide dropwise. After 15min, a solution of 1-tert-butyl 2-methyl (2S,4R)-4-hydroxy-1,2-pyrrolidinedicarboxylate in CH_2Cl_2 (20mL) was added at the same temperature.

The reaction mixture was warmed to 0℃, and then cooled to -70℃. Triethylamine (23mL) was added to the reaction mixture, and warmed to room temperature. The reaction mixture was quenched by adding water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 1N HCl and brine, dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo, the residue was purified with silica gel chromatography (n-hexane/ethyl acetate = 4/1 to 2/1) to give the target compound as a yellow oil (2.61g).

^{1}H-NMR (in $CDCl_3$) : δ 1.55-1.38(9H, m), 2.66-2.51(1H, m), 3.05-2.84(1H, m), 3.77(3H, s), 3.97-3.84(2H, m), 4.88-4.65(1H, m).

Example 8-2

1-tert-Butyl 2-methyl (2S)-4,4-difluoro-1,2-pyrrolidinedicarboxylate

To a solution of 1-tert-butyl 2-methyl (2S)-4-oxo-1,2-pyrrolidinedicarboxylate obtained in Example 8-1 (3.6g) in dichloromethane, was added diethylaminosulfur trifluoride (4mL) dropwise with cooling on an ice bath. The reaction mixture was warmed to room temperature and stirred for 11hrs.

To the resulting mixture was added $NaHCO_3$, and the reaction mixture was quenched by adding saturated aqueous $NaHCO_3$, and then water (1000mL) and $CaCl_2$ (11.5g) in water (50mL) were added. The resulting suspension was

extracted with ethyl acetate, the combined organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel chromatography (n-hexane/ethyl acetate = 5/1) to give the target compound as a yellow oil (3.6g).

^{1}H-NMR (in $CDCl_3$) : δ 1.53-1.36(9H, m), 2.55-2.35(1H, m), 2.83-2.58(1H, m), 3.94-3.71(5H, m), 4.62-4.37(1H, m).
MS (ESI+) : m/z 266.18 (M+H).

Example 8-3
(2S)-1-(tert-Butoxycarbonyl)-4,4-difluoro-2-pyrrolidinecarboxylic acid

The crude product of 1-tert-butyl 2-methyl (2S)-4,4-difluoro-1,2-pyrrolidinedicarboxylate obtained in Example 8-2 (3.9g) was dissolved in methanol (11mL) and then 1N NaOH (22mL) was added at room temperature.

After stirring for 1.5hrs, the resulting mixture was washed with diethyl ether, acidified with 1N HCl (30mL), and then was extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo. The residue was triturated with hexane to give the target compound as a white powder (3.1g).

^{1}H-NMR (in $CDCl_3$) : δ 1.62-1.30(9H, m), 2.92-2.39(2H, m), 4.02-3.60(2H, m), 4.69-4.41(1H, m), 7.50(1H, br-s).
MS (ESI-) : m/z 250.19 (M-H).

Example 8-4
tert-Butyl (2S)-2-aminocarbonyl-4,4-difluoro-1-pyrrolidinecarboxylate

To a solution of (2S)-1-(tert-butoxycarbonyl)-4,4-difluoro-2-pyrrolidinecarboxylic acid obtained in Example 8-3 in acetonitrile (30mL), were added 1-hydroxybenzotriazole hydrate (1.98g) and water soluble carbodiimide (3.11g) with cooling on an ice bath. After stirred for 20min, 28% aqueous NH_3 (2mL) was added at the same temperature and the resulting mixture was stirred for 1hr.

The reaction mixture was filtered and the filtration was evaporated in vacuo. After dilution with ethyl acetate, the resulting mixture was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and filtered. After removal of the solvent, the target compound was obtained as a yellow oil (3.2g).

^{1}H-NMR (in $CDCl_3$) : δ 1.48(9H, s), 3.10-2.44(2H, m), 4.02-3.54(2H, m), 4.65-4.41(1H, m), 5.71-5.40(1H, m), 6.97-6.64(1H, m).
MS (ESI+) : m/z 251.22 (M+H).

Example 8-5
(2S)-4,4-Difluoro-2-pyrrolidinecarboxamide hydrochloride

tert-Butyl (2S)-2-aminocarbonyl-4,4-difluoro-1-pyrrolidinecarboxylate obtained in Example 8-4 (3.2g) was dissolved in 4N HCl in dioxane (13mL) and the resulting mixture was stirred for 10min at room temperature.

After removal of the solvent, the resulting residue was triturated with ethyl acetate to give the target compound as a white powder (2.1g).

MS (ESI+) : m/z 150.95 (M+H).

Example 8-6

(2S)-1-Chloroacetyl-4,4-difluoro-2-pyrrolidinecarboxamide

To a mixture of (2S)-4,4-difluoro-2-pyrrolidinecarboxamide hydrochloride obtained in Example 8-5 and sodium 2-ethylhexanoate (4.35g) in tetrahydrofuran (30mL), was added chloroacetyl chloride with cooling on an ice bath. The reaction mixture was stirred for 30min at the same temperature.

The resulting mixture was then poured onto buchner funnel/filter paper and washed with ethyl acetate. The solvent was removed in vacuo and the residue was purified with silica gel chromatography (chloroform/methanol =10/1 to 5/1) to give the target compound as a colorless oil (2.27 g).

^{1}H-NMR (in $CDCl_3$) : δ 2.70-2.48(1H, m), 3.13-2.89(1H, m), 4.16-3.86(4H, m), 4.86-4.75(1H, m), 5.69(1H, br-s), 6.64(1H, br-s).

MS (ESI-) : m/z 225.15 (M-H).

Example 8-7

(2S)-1-Chloroacetyl-4,4-difluoro-2-pyrrolidinecarbonitrile

To a solution of (2S)-1-chloroacetyl-4,4-difluoro-2-pyrrolidinecarboxamide obtained in Example 8-6 (14.5g) in tetrahydrofuran (25mL), was added tetrafluoroacetic anhydride (2.3mL) at room temperature.

After stirring for 30min, the resulting mixture was concentrated in vacuo. The residue was purified with silica gel chromatography (n-hexane/ethyl acetate = 4/1 to 1/1) to give the target compound as a colorless solid (1.9g).

^{1}H-NMR (in $CDCl_3$) : δ 2.95-2.67(2H, m), 4.21-3.88(4H, m), 5.06-4.87(1H, m).

Example 8-8

(2S)-4,4-Difluoro-1-({[1-methyl-4-({[(1E)-3-pyridinylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (83mg) was prepared from nicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 1-5 and (2S)-1-chloroacetyl-4,4-difluoro-2-pyrrolidinecarbonitrile obtained in Example 8-7 in a similar manner to that of Example 7-2.

^{1}H-NMR (in DMSO) : δ 1.38(3H, s), 2.20-1.43(8H, m), 3.06-2.77(2H, m), 4.48-3.90(5H, m), 5.30-5.14(1H, m), 7.99-7.69(1H, m), 8.58-8.32(2H, m), 8.90-8.68(1H, m), 9.39-8.90(3H, m).

MS (ESI+) : m/z 406.21 (M+H).

Example 9-1

6-Trifluoromethylnicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime

The title compound (65mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-6-trifluoromethyl-3-pyridinyl-methylidene]amino}oxy)cyclohexylcarbamate in a similar manner to that of Example 17-2 described later.

MS (ESI+) : m/z 302.14 (M+H).

Example 9-2

(2S)-4,4-difluoro-1-[({1-methyl-4-[({(1E)-[6-(trifluoromethyl)-3-pyridinyl]methylidene}amino)oxy]cyclohexy

1}amino)acetyl]-2-pyrrolidinecarbonitrile dihydrochloride

The title compound (5.5mg) was prepared from (2S)-1-chloroacetyl-4,4-difluoro-2-pyrrolidinecarbonitrile obtained in Example 8-7 and 6-trifluoromethylnicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 9-1 in a similar manner to that of Example 7-2.

^{1}H-NMR (in DMSO) : δ 1.36(3H, s), 1.69-1.43(2H, m), 1.99-1.69(4H, m), 2.20-1.99(2H, m), 3.05-2.78(2H, m), 4.64-3.82(5H, m), 5.31-5.12(1H, m), 8.06-7.90(1H, m), 8.37-8.19(1H, m), 8.50-8.37(1H, m), 9.22-8.90(3H, m).
MS (ESI+) : m/z 474.11 (M+H).

Example 10

(2S)-4,4-Difluoro-1-({[1-methyl-4-({[(1E)-1-(3-pyridinyl)ethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile dihydrochloride

The title compound (42.1mg) was prepared from 1-methyl-4-({[(1E)-1-(3-pyridinyl)ethylidene]amino}oxy)cyclohexylamino and (2S)-1-chloroacetyl-4,4-difluoro-2-pyrrolidinecarbonitrile obtained in Example 8-7 in a similar manner to that of Example 7-2.

^{1}H-NMR (in DMSO) : δ 1.38(3H, s), 2.20-1.44(8H, m), 2.27(3H, s), 3.03-2.78(2H, m), 4.49-3.91(5H, m), 5.29-5.13(1H, m), 8.00-7.82(1H, m), 8.66-8.50(1H, m), 8.90-8.78(1H, m), 9.32-9.00(3H, m).
MS (ESI+) : m/z 420.21 (M+H).

Example 11

(2S)-4,4-Difluoro-1-[({1-methyl-4-[(2-pyridinylmethox

y)imino]cyclohexyl}amino)acetyl]-2-pyrrolidinecarbonitrile dihydrochloride

The title compound (249mg) was prepared from 1-methyl-4-[(2-pyridinylmethoxy)imino]cyclohexyl}amino and (2S)-1-chloroacetyl-4,4-difluoro-2-pyrrolidinecarbonitrile obtained in Example 8-7 in a similar manner to that of Example 7-2.

^{1}H-NMR (in DMSO) : δ 1.44(3H, s), 2.36-1.74(7H, m), 3.02-2.74(3H, m), 3.27-3.09(1H, m), 4.46-4.04(4H, m), 5.27-5.15(1H, m), 5.37(2H, s), 8.01-7.80(2H, m), 8.52-8.38(1H, m), 8.90-8.76(1H, m), 9.32-9.11(1H, m), 9.54-9.32(1H, m).
MS (ESI+) : m/z 406.23 (M+H).

Example 12-1
tert-Butyl 1-methyl-4-({[(1E)-4-pyridinylmethylidene]amino}oxy)cyclohexylcarbamate

To a cold (-78℃) stirred solution of tert-butyl [trans-4-aminooxy-1-methylcyclohexyl]carbamate (147mg) in methanol (1mL), was added isonicotinaldehyde (0.057mL). The mixture was stirred to room temperature for 16hrs. The solution was concentrated in vacuo. The residue was triturated with isopropylether, then filtrated to provide the target compound as a white solid (128mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.45(9H, s), 1.57-1.94(8H, m), 4.35(1H, br-s), 4.39(1H, br-s), 7.45(2H, dd, J=1.5, 4.4Hz), 8.04(1H, s), 8.62(2H, dd, J=1.5, 4.4Hz).
MS (ES+) : m/e 334.22.

Example 12-2
Isonicotinaldehyde O-(4-amino-4-methylcyclohexyl)-oxime bis(trifluoroacetate)

The title compound (165mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-4-pyridinylmethylidene]amino}oxy)cyclohexylcarbamate obtained in Example 12-1 in a similar manner to that of Example 7-1.

Example 12-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-4-pyridinylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (89.0mg) was prepared from isonicotinaldehyde O-(4-amino-4-methylcyclohexyl)-oxime bis(trifluoroacetate) obtained in Example 12-2 and (2S)-1-chloroacetyl-4,4-difluoro-2-pyrrolidinecarbonitrile obtained in Example 8-7 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.15(3×1/5H, s), 1.39-1.80(6H, m), 1.97(2H, br-s), 2.20-2.57(1H, m), 2.70(1×4/5H, t), 2.77(1×1/5H, t), 3.30-4.40(4H, m), 4.31(1H, br-s), 4.97(1×4/5H, d, J=9.3Hz), 5.09(1×1/5H, d, J=9.0Hz), 5.37(1×1/5H, br-d, J=53.2Hz), 5.44(1×4/5H, br-t, J=3.6, 50.8Hz), 7.45(2H, dd, J=1.7, 4.6Hz), 8.03(1H, s), 8.62(2H, dd, J=1.7, 4.6Hz).
MS (ES+) : m/e 388.15.

Example 13-1
tert-Butyl 4-({[(1E)-(6-chloro-3-pyridinyl)-methylidene]amino}oxy)-1-methylcyclohexylcarbamate

The title compound (138mg) was prepared from

tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 6-chloronicotinaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.44(9H, s), 1.63-1.95(8H, m), 4.32(1H, br-s), 4.38(1H, br-s), 7.33(1H, d, J=8.3Hz), 7.95(1H, dd, J=2.3, 8.3Hz), 8.07(1H, s), 8.47(1H, d, J=2.3Hz).
MS (ES+) : m/e 368.13.

Example 13-2
6-Chloronicotinaldehyde O-(4-amino-4-methyl-cyclohexyl)oxime bis(trifluoroacetate)

The title compound (146mg) was prepared from tert-butyl 4-({[(1E)-(6-chloro-3-pyridinyl)-methylidene]amino}oxy)-1-methylcyclohexylcarbamate obtained in Example 13-1 in a similar manner to that of Example 7-1.

Example 13-3
(2S,4S)-1-({[4-({[(1E)-(6-Chloro-3-pyridinyl)methylidene]amino}oxy)-1-methylcyclohexyl]amino}acetyl)-4-fluoro-2-pyrrolidinecarbonitrile

The title compound (13.3mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 6-chloronicotinaldehyde O-(4-amino-4-methyl-cyclohexyl)oxime bis(trifluoroacetate) obtained in Example 13-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.11(3×4/5H, s), 1.15(3×1/5H, s), 1.38-1.76(6H, m), 1.96(2H, br-s), 2.20-2.58(1H, m), 2.70(1×4/5H, t), 2.77(1×1/5H, t), 3.30-4.10(4H, m),

4.28(1H, br-s), 4.97(1×4/5H, d, J=9.2Hz), 5.09(1×1/5H, d, J=9.0Hz), 5.37(1×1/5H, br-d, J=51.0Hz), 5.44(1×4/5H, br-d, J=51.0Hz), 7.33(1H, d, J=8.4Hz), 7.96(1H, dd, J=2.4, 8.4Hz), 8.07(1H, s), 8.47(1H, d, J=2.4Hz).
MS (ES+) : m/e 422.09.

Example 14-1
tert-Butyl 4-({[(1E)-(6-methoxy-3-pyridinyl)-methylidene]amino}oxy)-1-methylcyclohexylcarbamate

The title compound (141mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 6-methoxynicotinaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.44(9H, s), 1.60-1.90(8H, m), 3.96(3H, s), 4.27(1H, br-s), 4.39(1H, br-s), 6.75(1H, d, J=8.6Hz), 7.94(1H, dd, J=2.2, 8.6Hz), 8.05(1H, s), 8.18(1H, d, J=2.2Hz).
MS (ES+) : m/e 364.19.

Example 14-2
6-Methoxynicotinaldehyde O-(4-amino-4-methyl-cyclohexyl)oxime bis(trifluoroacetate)

The title compound (163mg) was prepared from tert-butyl 4-({[(1E)-(6-methoxy-3-pyridinyl)-methylidene]amino}oxy)-1-methylcyclohexylcarbamate obtained in Example 14-1 in a similar manner to that of Example 7-1.

Example 14-3
(2S,4S)-4-Fluoro-1-({[4-({[(1E)-(6-methoxy-3-pyridinyl)methylidene]amino}oxy)-1-methylcyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (74.4mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 6-methoxynicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 14-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.11(3×4/5H, s), 1.15(3×1/5H, s), 1.30-1.78(6H, m), 1.95(2H, br-s), 2.30-2.56(1H, m), 2.69(1×4/5H, t, J=15.8Hz), 2.77(1×1/5H, t, J=15.5Hz), 3.30-4.02(4H, m), 3.96(3H, s), 4.23(1H, br-s), 4.97(1×4/5H, d, J=9.6Hz), 5.12(1×1/5H, d, J=9.5Hz), 5.36(1×1/5H, br-d, J=51.1Hz), 5.44(1×4/5H, br-d, J=3.4, 51.1Hz), 6.75(1H, d, J=8.6Hz), 7.95(1H, dd, J=2.4, 8.6Hz), 8.05(1H, s), 8.18(1H, d, J=2.4Hz).
MS (ES+) : m/e 418.12.

Example 15-1
tert-Butyl 1-methyl-4-({[(1E)-(6-phenoxy-3-pyridinyl)methylidene]amino}oxy)cyclohexylcarbamate

The title compound (203mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 6-phenoxynicotinaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.44(9H, s), 1.62-1.90(8H, m), 4.28(1H, br-s), 4.39(1H, br-s), 6.91(1H, d, J=8.7 Hz), 7.15(2H, d, J=7.5Hz), 7.23(1H, t, J=7.5Hz), 7.42(2H, t, J=7.5Hz), 8.04(1H, dd, J=2.1, 8.7Hz), 8.06(1H, s), 8.22(1H, d, J=2.1Hz).
MS (ES+) : m/e 426.16.

Example 15-2

6-Phenoxynicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

The title compound (233mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-(6-phenoxy-3-pyridinyl)methylidene]amino}oxy)cyclohexylcarbamate obtained in Example 15-1 in a similar manner to that of Example 7-1.

Example 15-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-(6-phenoxy-3-pyridinyl)methylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (35.9mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 6-phenoxynicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 15-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.11(3×1/5H, s), 1.15(3×4/5H, s), 1.37-1.78(6H, m), 1.95(2H, br-s), 2.20-2.55(1H, m), 2.70(1×4/5H, t, J=15.3Hz), 2.77(1×1/5H, t, J=15.2Hz), 3.30-4.10(4H, m), 4.25(1H, br-s), 4.97(1×4/5H, d, J=9.0Hz), 5.10(1×1/5H, d, J=9.0Hz), 5.36(1×1/5H, br-d, J=51.0Hz), 5.44(1×4/5H, br-d, J=50.4Hz), 6.92(1H, d, J=8.4Hz), 7.14(2H, d, J=7.9Hz), 7.23(1H, t, J=7.9Hz), 7.42(2H, t, J=7.9Hz), 8.04(1H, br-d, J=8.4Hz), 8.06(1H, s), 8.22(1H, s).
MS (ES+) : m/e 480.06.

Example 16-1
tert-Butyl 1-methyl-4-[({(1E)-[6-(trifluoromethyl)-3-pyridinyl]methylidene}amino)oxy]cyclohexylcarbamate

The title compound (206mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 6-trifluoromethylnicotinaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.45(9H, s), 1.60-1.95(8H, m), 4.38(2H, br-s), 8.68(1H, d, J=8.4Hz), 8.12(1H, br-d, J=8.4Hz), 8.15(1H, s), 8.84(1H, br-s).
MS (ES+) : m/e 346.21(M-tBu).

Example 16-2
6-(Trifluoromethyl)nicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

The title compound (133mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-(6-Trifluoromethyl-3-pyridinyl)methylidene]amino}oxy)cyclohexylcarbamate obtained in Example 16-1 in a similar manner to that of Example 7-1.

Example 16-3
(2S,4S)-4-Fluoro-1-[({1-methyl-4-[({(1E)-[6-(trifluoromethyl)-3-pyridinyl]methylidene}amino)oxy]cyclohexyl}amino)acetyl]-2-pyrrolidinecarbonitrile

The title compound (23mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 6-(trifluoromethyl)nicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 16-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.15(3×1/5H,

s), 1.37-1.80(6H, m), 1.97(2H, br-s), 2.20-2.55(1H, m), 2.70(1×4/5H, t, J=15.2Hz), 2.77(1×1/5H, t, J=15.5Hz), 3.30-4.10(4H, m), 4.33(1H, br-s), 4.97(1×4/5H, d, J=9.3Hz), 5.08(1×1/5H, d, J=9.5Hz), 5.36(1×1/5H, br-d, J=51.0Hz), 5.44(1×4/5H, br-t, J=3.6, 51.5Hz), 7.88(1H, d, J=8.2Hz), 8.12(1H, d, J=8.2Hz), 8.15(1H, s), 8.84(1H, br-s).

MS (ES+) : m/e 456.08.

Example 17-1

tert-Butyl 1-methyl-4-{[(1E)-1-(3-pyridinyl)-ethylidene]amino}oxy}cyclohexylcarbamate

The title compound was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)carbamate and 3-acetylpyridine in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36(3H, s), 1.45(9H, s), 1.66-1.90(8H, m), 2.26(3H, s), 4.35(1H, br-s), 4.40(1H, br-s), 7.29(1H, dd, J=4.7, 8.1Hz), 7.96(1H, ddd, J=1.7, 2.4, 8.1Hz), 8.58(1H, dd, J=1.7, 4.7Hz), 8.87(1H, d, J=2.4 Hz).

MS (ES+) : m/e 348.31.

Example 17-2

(1E)-1-(3-pyridinyl)ethanone O-(4-amino-4-methyl-cyclohexyl)oxime

To a cold stirred solution of tert-Butyl 1-methyl-4-{[(1E)-1-(3-pyridinyl)-ethylidene]amino}oxy}cyclohexylcarbamate (50mg) in methanol (0.5mL), was added 4N HCl solution in dioxane (1.0mL). The mixture was stirred for 2hrs, and alkalized with saturated aqueous $NaHCO_3$, then extracted with chloroform. The combined

organic layer was dried and filtrated. The filtrate was concentrated in vacuo to provide the target compound as an oil (30mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.17(3H, s), 1.30-1.80(6H, m), 1.90-2.03(2H, m), 2.25(3H, s), 4.22-4.33(1H, m), 7.28(1H, dd, J=4.9, 8.2Hz), 7.97(1H, dd, J=2.0, 8.2Hz), 8.58(1H, dd, J=2.0, 4.9Hz), 8.87(1H, d, J=2.0Hz).
MS (ES+) : m/e 248.23.

Example 17-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-1-(3-pyridinyl)ethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (40mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and (1E)-1-(3-pyridinyl)ethanone O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 17-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.16(3×1/5H, s), 1.40-1.80(6H, m), 1.96(2H, br-s), 2.19-2.56(1H, m), 2.26(3H, s), 2.70(1×4/5H, t, J=15.3Hz), 2.76(1×1/5H, t, J=15.2Hz), 3.30-4.12(4H, m), 4.30(1H, br-s), 4.97(1×4/5H, d, J=9.2Hz), 5.12(1×1/5H, d, J=9.2Hz), 5.36(1×1/5H, br-d, J=51.1Hz), 5.44(1×4/5H, br-t, J=3.3, 51.1Hz), 7.29(1H, ddd, J=0.9, 4.8, 8.1Hz), 7.97(1H, ddd, J=1.7, 2.2 8.1Hz), 8.58(1H, dd, J=1.7, 4.8Hz), 8.87(1H, dd, J=0.9, 2.2Hz).
MS (ES-) m/e 402.23.

Example 18-1
tert-Butyl 1-methyl-4-({[(1E)-(6-methyl-2-pyridinyl)-

methylidene]amino}oxy)cyclohexylcarbamate

The title compound was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)carbamate and 6-mehtyl-2-pyridinecarboxaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.44(9H, s), 1.62-1.90(8H, m), 2.56(3H, s), 4.36(2H, br-s), 7.11(1H, br-d, J=7.5Hz), 7.57(1H, t, J=7.5Hz), 7.62(1H, br-d, J=7.5Hz), 8.16(1H, s).
MS (ES+) : m/e 348.32.

Example 18-2
6-Methyl-2-pyridinecarbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

The title compound (158mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-(6-methyl-2-pyridinyl)-methylidene]amino}oxy)cyclohexylcarbamate obtained in Example 18-1 in a similar manner to that of Example 7-1.

Example 18-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-(6-methyl-2-pyridinyl)methylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (85.5mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 6-methyl-2-pyridinecarbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 18-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.11(3×4/5H, s), 1.15(3×1/5H,

s), 1.46(2H, br-s), 1.55-1.80(4H, m), 1.96(2H, br-s), 2.17-2.50(1H, m), 2.57(3H, s), 2.70(1×4/5H, t, J=15.8Hz), 2.76(1 × 1/5H, t, J=14.7Hz), 3.30-4.15(4H, m), 4.23-4.37(1H, m), 4.97(1×4/5H, d, J=9.3Hz), 5.12(1× 1/5H, d, J=9.0Hz), 5.36(1×1/5H, br-d, J=51.0Hz), 5.44(1 × 4/5H, br-t, J=3.5, 51.0Hz), 7.11(1H, d, J=7.7Hz), 7.57(1H, t, J=7.7Hz), 7.63(1H, t, J=7.7Hz), 8.16(1H, s).
MS (ES+) : m/e 402.24.

Example 19-1
tert-Butyl 1-methyl-4-({[(1E)-(3-methyl-4-pyridinyl)-methylidene]amino}oxy)cyclohexylcarbamate

The title compound (194mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 3-mehtyl-4-pyridinecarboxaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.45(9H, s), 1.60-1.92(8H, m), 2.41(3H, s), 4.36(1H, br-s), 4.40(1H, br-s), 7.54(1H, d, J=5.1Hz), 8.27(1H, s), 8.44(1H, d, J=5.1Hz), 8.46(1H, s).
MS (ES+) : m/e 348.32.

Example 19-2
3-Methylisonicotinaldehyde O-(4-amino-4-methyl-cyclohexyl)oxime bis(trifluoroacetate)

The title compound (121mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-(3-methyl-4-pyridinyl)-methylidene]amino}oxy)cyclohexylcarbamate obtained in Example 19-1 in a similar manner to that of Example 7-1.

Example 19-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-(3-methyl-4-

pyridinyl)methylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (48.2mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 3-methylisonicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 19-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.16(3×1/5H, s), 1.36-1.80(6H, m), 1.98(2H, br-s), 2.20-2.56(1H, m), 2.40(3H, s), 2.70(1×4/5H, t, J=16.4Hz), 2.77(1×1/5H, t, J=14.9Hz), 3.30-4.10(4H, m), 4.31(1H, br-s), 4.97(1×4/5H, d, J=9.2Hz), 5.09(1×1/5H, d, J=8.6Hz), 5.36(1×1/5H, br-d, J=51.7Hz), 5.44(1×4/5H, br-d, J=3.5, 51.1Hz), 7.54(1H, d, J=5.0Hz), 8.28(1H, s), 8.43(1H, d, J=5.0Hz), 8.45(1H, s).
MS (ES+) : m/e 402.25.

Example 20-1
tert-Butyl 1-methyl-4-({[(1E)-(1,3-thiazol-2-yl)-methylidene]amino}oxy)cyclohexylcarbamate

The title compound (208mg) was prepared from tert-butyl [trans-4-(aminooxy)-1-methylcyclohexyl]-carbamate and 2-thiazolecarboxaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.45(9H, s), 1.60-1.90(8H, m), 4.36(2H, br-s), 7.32(1H, dd, J=0.9, 3.1Hz), 7.86(1H, d, J=3.1Hz), 8.32(1H, d, J=0.9Hz).
MS (ES+) : m/e 340.21.

Example 20-2

1,3-Thiazole-2-carbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

The title compound (138mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-(1,3-thiazol-2-yl)-methylidene]amino}oxy)cyclohexylcarbamate obtained in Example 20-1 in a similar manner to that of Example 7-1.

Example 20-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-(1,3-thiazol-2-yl)methylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (12.4mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 1,3-thiazole-2-carbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 20-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.16(3×1/5H, s), 1.38-1.80(6H, m), 1.97(2H, br-s), 2.20-2.57(1H, m), 2.70(1×4/5H, t, J=15.5Hz), 2.77(1×1/5H, t, J=15.2Hz), 3.30-4.10(4H, m), 4.31(1H, br-s), 4.97(1×4/5H, d, J=9.0Hz), 5.09(1×1/5H, d, J=9.0Hz), 5.36(1×1/5H, br-d, J=51.5Hz), 5.44(1×4/5H, br-d, J=51.5Hz), 7.32(1H, d, J=3.2Hz), 7.86(1H, d, J=3.2Hz), 8.32(1H, s).
MS (ES+) : m/e 394.10.

Example 21-1
tert-Butyl trans-4-[(cyclohexylideneamino)oxy]-1-methylcyclohexylcarbamate

The title compound (81.5mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-

carbamate and cyclohexanone in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.33(3H, s), 1.44(9H, s), 1.55-1.85(14H, m), 2.20(2H, br-t, J=6.3Hz), 2.48(2H, br-s), 4.14(1H, br-s), 4.38(1H, br-s).
MS (ES+) : m/e 325.33.

Example 21-2
Cyclohexanone O-(4-amino-4-methylcyclohexyl)oxime

To tert-butyl {trans-4-[(cyclohexylideneamino)-oxy]-1-methylcyclohexyl}carbamate obtained in Example 21-1 (81.5mg), was added trifluoroacetic acid (0.5mL) at room temperature for 10min. The mixture was alkalized with saturated aqueous $NaHCO_3$, then extracted with chloroform. The combined organic layer was dried and filtrated. The filtrate was concentrated in vacuo to provide the target compound as an oil (70.7mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.31(3H, s), 1.45-2.05(14H, m), 2.19(2H, t, J=6.4Hz), 2.45(2H, br-s), 4.05(1H, br-s).

Example 21-3
(2S,4S)-1-[({4-[(Cyclohexylideneamino)oxy]-1-methylcyclohexyl}amino)acetyl]-4-fluoro-2-pyrrolidinecarbonitrile

The title compound (26.3mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and cyclohexanone O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 21-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.10(3×4/5H, s), 1.13(3×1/5H,

s), 1.33-1.48(2H, m), 1.50-1.72(10H, m), 1.82-1.98(2H, m), 2.18-2.58(1H, m), 2.20(2H, br-t, J=6.0Hz), 2.48(2H, br-s), 2.69(1×4/5H, t, J=15.6Hz), 2.75(1×1/5H, t, J=15.6Hz), 3.28-4.05(4H, m), 4.07(1H, br-s), 4.96(1×4/5H, d, J=9.4Hz), 5.16(1×1/5H, d, J=9.4Hz), 5.35(1×1/5H, br-d, J=51.5Hz), 5.43(1×4/5H, br-d, J=51.5Hz).
MS (ES+) : m/e 379.24.

Example 22-1
tert-Butyl 1-methyl-4-{[(1-methylethylidene)amino]-oxy}cyclohexylcarbamate

The title compound (72mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and acetone in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.33(3H, s), 1.44(9H, s), 1.60-1.85(8H, m), 1.87(3H, s), 1.88(3H, s), 4.14(1H, br-s), 4.37(1H, br-s).
MS (ES+) : m/e 285.32.

Example 22-2
Acetone O-(4-amino-4-methylcyclohexyl)oxime

The title compound (33.2mg) was prepared from tert-butyl 1-methyl-4-{[(1-methylethylidene)amino]-oxy}cyclohexylcarbamate obtained in Example 22-1 in a similar manner to that of Example 17-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.14(3H, s), 1.15-1.48(4H, m), 1.50-1.76(4H, m), 1.86(3H, s), 1.87(3H, s), 4.07(1H, br-s).
MS (ES+) : m/e 185.13.

Example 22-3
(2S,4S)-4-Fluoro-1-{[(1-methyl-4-{[(1-methylethylidene)amino]oxy}cyclohexyl)amino]acetyl}-2-pyrrolidinecarbonitrile

The title compound (30.6mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and acetone O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 22-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.10(3×4/5H, s), 1.15(3×1/5H, s), 1.32-1.48(2H, m), 1.50-1.70(4H, m), 1.72-2.00(2H, m), 1.86(3H, s), 1.87(3H, s), 2.18-2.56(1H, m), 2.69(1×4/5H, t, J=15.0Hz), 2.75(1×1/5H, t, J=15.3Hz), 3.30-4.10(4H, m), 4.08(1H, br-s), 4.97(1×4/5H, d, J=9.5Hz), 5.16(1×1/5H, d, J=9.5Hz), 5.35(1×1/5H, br-d, J=50.9Hz), 5.43(1×4/5H, br-d, J=51.5Hz).
MS (ES+) m/e 339.24.

Example 23-1
tert-Butyl 1-methyl-4-({[(1E)-2-thienylmethylidene]-amino}oxy)cyclohexylcarbamate

The title compound (64.8mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 2-thiophenecarboxaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.34(3H, s), 1.44(9H, s), 1.60-2.00(8H, m), 4.28(1H, br-s), 4.38(1H, br-s), 7.03(1H, dd, J=3.7, 5.1Hz), 7.16(1H, d, J=3.7Hz), 7.30(1H, d, J=5.1Hz), 8.25(1H, s).
MS (ES+) : m/e 339.20.

Example 23-2

2-Thiophenecarbaldehyde O-(4-amino-4-methylcyclohexyl)oxime

The title compound (34.5mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-2-thienylmethylidene]amino}oxy)cyclohexylcarbamate obtained in Example 23-1 in a similar manner to that of Example 17-2.

Example 23-3

(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-2-thienylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile hydrochloride

To a stirred solution of 2-thiophenecarbaldehyde O-(trans-4-amino-4-methylcyclohexyl)oxime obtained in Example 23-2 (34.1mg) in dimethylformamide (1.5mL), were added K_2CO_3 (37.7mg), (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 (26.0mg) and sodium iodide (1mg).

The mixture was stirred for 5hrs at 50℃ and diluted with water. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried, and concentrated in vacuo. The residue was dissolved to ethyl acetate, then added 4M HCl in dioxane (30μL). The precipitate was filtrated, then washed with ethyl acetate to provide the target compound as a white solid (22.5mg).

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36(3H, s), 1.40-1.65(2H, m), 1.70-2.17(6H, m), 2.35-2.60(2H, m), 3.36(2H, s), 3.68-4.29(4H, m), 5.09 (1H, d, J=8.3Hz), 5.58(1H, br-d, J=52.2Hz), 7.17(1H, dd, J=3.7, 5.0Hz), 7.55(1H, d, J=3.7Hz), 7.82(1H, d, J=5.0Hz), 8.96(2H, br-s).

MS (ES+) : m/e 393.17.

Example 24-1

tert-Butyl 1-methyl-4-({[(1E)-phenylmethylidene]-amino}oxy)cyclohexylcarbamate

The title compound (314mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and benzaldehyde in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.45(9H, s), 1.50-2.20(8H, m), 4.31(1H, br-s), 4.39(1H, br-s), 7.33-7.40(3H, m), 7.62-7.55(2H, m), 8.10(1H, s).
MS (ES+) : m/e 333.26.

Example 24-2

Benzaldehyde O-(4-amino-4-methylcyclohexyl)oxime

The title compound (206mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-phenylmethylidene]-amino}oxy)cyclohexylcarbamate obtained in Example 24-1 in a similar manner to that of Example 17-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.16(3H, s), 1.30-1.43(2H, m), 1.58-1.80(4H, m), 1.86-2.04(2H, m), 4.18-4.30(1H, m), 7.30-7.42(3H, m), 7.52-7.64(2H, m), 8.09 (1H, s).
MS (ES+) : m/e 233.32.

Example 24-3

(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-phenylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (92.3mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonit

rile obtained in Preparation 1-8 and benzaldehyde O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 24-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×5/4H, s), 1.15(3×1/5H, s), 1.39-1.52(2H, m), 1.52-1.49(4H, m), 1.97(2H, br-s), 2.19-2.56(1H, m), 2.69(1×4/5H, t, J=15.7Hz), 2.76(1×1/5H, t, J=15.7Hz), 3.28-4.12(4H, m), 4.26(1H, br-s), 4.97(1×4/5H, d, J=9.1Hz), 5.13(1×1/5H, d, J=9.0Hz), 5.36(1×1/5H, br-dt, J=3.4, 51.3Hz), 5.44(1×4/5H, br-dt, J=3.4, 51.1Hz), 7.33-7.43(3H, m), 7.54-7.63(2H, m), 8.09(1H, s).
MS (ES+) : m/e 387.18.

Example 25-1
tert-Butyl 1-methyl-4-({[(1E)-1-phenylethylidene]-amino}oxy)cyclohexylcarbamate

The title compound (222mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and acetophenone in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.36(3H, s), 1.45(9H, s), 1.62-1.90(8H, m), 2.25(3H, s), 4.34(1H, br-t, J=4.5Hz), 4.40(1H, br-s), 7.32-7.41(3H, m), 7.60-7.69(2H, m.
MS (ES+) m/e 347.27.

Example 25-2
(1E)-1-Phenylethanone O-(4-amino-4-methylcyclohexyl)-oxime

The title compound (68.5mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-1-phenylethylidene]-amino}oxy)cyclohexylcarbamate obtained in Example 25-1

in a similar manner to that of Example 17-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.17(3H, s), 1.32-1.45(2H, m), 1.56-1.80(4H, m), 1.90-2.04(2H, m), 2.24(3H, s), 4.20-4.32(1H, m), 7.30-7.40(3H, m), 7.60-7.70(2H, m).
MS (ES+) : m/e 247.24.

Example 25-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-1-phenylethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (58.7mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and (1E)-1-phenylethanone O-(4-amino-4-methylcyclohexyl)-oxime obtained in Example 25-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.16(3×1/5H, s), 1.30-1.80(6H, m), 1.96(2H, br-s), 2.15-2.55(1H, m), 2.25(3H, s), 2.69(1×4/5H, t, J=15.7Hz), 2.76(1×1/5H, t, J=15.7Hz), 3.31-4.40(4H, m), 4.28(1H, br-s), 4.97(1×4/5H, d, J=9.0Hz), 5.15(1×1/5H, d, J=9.0Hz), 5.35(1×1/5H, br-d, J=51.1Hz), 5.44(1×4/5H, br-t, J=3.7, 51.5Hz), 7.32-7.40(3H, m), 7.60-7.70(2H, m).
MS (ES+) : m/e 401.28.

Example 26-1
tert-Butyl 1-methyl-4-({[(1E)-5-pyrimidinylmethylidene]amino}oxy)cyclohexylcarbamate

The title compound (84.8mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 5-pyrimidinecarbaldehyde in a similar

manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.35(3H, s), 1.45(9H, s), 1.61-1.92(8H, m), 4.36(2H, br-s), 8.07(1H, s), 8.92(2H, s), 9.18(1H, s).
MS (ES+) m/e 335.23.

Example 26-2
5-Pyrimidinecarbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate)

The title compound (147mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-5-pyrimidinylmethylidene]amino}oxy)cyclohexylcarbamate obtained in Example 26-1 in a similar manner to that of Example 7-1.

Example 26-3
(2S,4S)-4-Fluoro-1-({[1-methyl-4-({[(1E)-5-pyrimidinylmethylidene]amino}oxy)cyclohexyl]amino}acetyl)-2-pyrrolidinecarbonitrile

The title compound (22.4mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 5-pyrimidinecarbaldehyde O-(4-amino-4-methylcyclohexyl)oxime bis(trifluoroacetate) obtained in Example 26-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.12(3×4/5H, s), 1.15(3×1/5H, s), 1.40-1.80(6H, m), 1.97(2H, br-s), 2.18-2.60(1H, m), 2.70(1×4/5H, t, J=15.6Hz), 2.77(1×1/5H, t, J=15.6Hz), 3.30-4.09(4H, m), 4.32(1H, br-s), 4.96(1×4/5H, d, J=9.4Hz), 5.08(1×1/5H, d, J=9.4Hz), 5.36(1×1/5H, br-d, J=51.5Hz), 5.45(1×4/5H, br-d, J=50.5Hz), 8.06(1H, s), 8.92(2H, s), 9.18(1H, s).

MS (ES+) : m/e 389.18.

Example 27-1
tert-Butyl 4-[(cyclopentylideneamino)oxy]-1-methylcyclohexylcarbamate

The title compound (304mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and cyclopentanone in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.33(3H, s), 1.43(9H, s), 1.60-1.83(12H, m), 2.32-2.44(4H, m), 4.14(1H, br-s), 4.37(1H, br-s).
MS (ES+) : m/e 311.28.

Example 27-2
Cyclopentanone O-(4-amino-4-methylcyclohexyl)oxime

The title compound (137mg) was prepared from tert-butyl 4-[(cyclopentylideneamino)oxy]-1-methylcyclohexylcarbamate obtained in Example 27-1 in a similar manner to that of Example 17-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.15(3H, s), 1.24-1.40(2H, m), 1.44-1.68(4H, m), 1.68-1.80(4H, m), 1.82-1.96(2H, m), 2.30-2.44(4H, m), 4.01-4.12(1H, m).
MS (ES+) : m/e 211.21.

Example 27-3
(2S,4S)-1-[({4-[(Cyclopentylideneamino)oxy]-1-methylcyclohexyl}amino)acetyl]-4-fluoro-2-pyrrolidinecarbonitrile

The title compound (15mg) was prepared from

(2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and cyclopentanone O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 27-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.11(3×4/5H, s), 1.14(3×1/5H, s), 1.35-1.50(2H, m), 1.50-1.69(4H, m), 1.69-1.80(4H, m), 1.83-1.97(2H, m), 2.19-2.42(5H, m), 2.69(1×4/5H, t, J=16.0Hz), 2.75(1×1/5H, t, J=16.1Hz), 3.30-4.02(4H, m), 4.08(1H, br-s), 4.95(1×4/5H, d, J=9.7Hz), 5.15(1×1/5H, d, J=9.5Hz), 5.35(1×1/5H, br-d, J=52.1Hz), 5.43(1×4/5H, br-dt, J=3.5, 51.5Hz).
MS (ES+) : m/e 365.24.

Example 28-1
tert-Butyl 4-{[(1-ethylpropylidene)amino]oxy}-1-methylcyclohexylcarbamate

The title compound (121mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-carbamate and 3-pentanone in a similar manner to that of Example 12-1.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.07(3H, t, J=7.7Hz), 1.08(3H, t, J=7.5Hz), 1.33(3H, s), 1.44(9H, s), 1.58-1.99(8H, m), 2.19(2H, q, J=7.5Hz), 2.31(2H, q, J=7.7Hz), 4.13(1H, br-s), 4.37(1H, br-s).
MS (ES+) : m/e 313.28.

Example 28-2
3-Pentanone O-(4-amino-4-methylcyclohexyl)oxime

The title compound (74.4mg) was prepared from tert-butyl 4-{[(1-ethylpropylidene)amino]oxy}-1-methylcyclohexylcarbamate obtained in Example 28-1 in a

similar manner to that of Example 17-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.06(3H, t, J=7.7Hz), 1.08(3H, t, J=7.5Hz), 1.13(3H, s), 1.20-1.70(8H, m), 1.80-1.93(2H, m), 2.19(2H, q, J=7.5Hz), 2.32(2H, q, J=7.7Hz), 4.00-4.12(1H, m).
MS (ES+) : m/e 213.19.

Example 28-3
(2S,4S)-1-{[(4-{[(1-Ethylpropylidene)amino]oxy}-1-methylcyclohexyl)amino]acetyl}-4-fluoro-2-pyrrolidinecarbonitrile

The title compound (60.5mg) was prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 3-pentanone O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 28-2 in a similar manner to that of Example 7-2.

^{1}H-NMR (300MHz, $CDCl_3$) : δ 1.07(3H, t, J=7.7Hz), 1.08(3H, t, J=7.5Hz), 1.09(3 × 4/5H, s), 1.13(3 × 1/5H, s), 1.33-1.48(2H, m), 1.50-1.68(4H, m), 1.78-1.96(2H, m), 2.13-2.57(1H, m), 2.19(2H, q, J=7.5Hz), 2.32(2H, q, J=7.7Hz), 2.69(1×4/5H, t, J=15.6Hz), 2.75(1×1/5H, t, J=15.9Hz), 3.27-4.13(5H, m), 4.96(1×4/5H, d, J=9.4Hz), 5.15(1×1/5H, d, J=9.4Hz), 5.35(1×1/5H, br-d, J=51.1Hz), 5.43(1×4/5H, br-t, J=3.3, 51.1Hz).
MS (ES+) : m/e 367.32.

Example 29-1
tert-Butyl 1-methyl-4-({[(1E)-2-pyridinylmethylidene]amino}oxy)cyclohexylcarbamate

The title compound (436mg) was prepared from tert-butyl (trans-4-aminooxy-1-methylcyclohexyl)-

carbamate and 2-pyridinecarboxaldehyde in a similar manner to that of Example 12-1.

Example 29-2

2-Pyridinecarboxaldehyde O-(4-amino-4-methylcyclohexyl)oxime

The title compound is prepared from tert-butyl 1-methyl-4-({[(1E)-2-pyridinyl-methylidene]amino}oxy)cyclohexylcarbamate obtained in Example 29-1 in a similar manner to that of Example 17-2.

Example 29-3

(2S,4S)-1-{[(4-{[(2-pyridinylmethylidene)amino]oxy}-1-methylcyclohexyl)amino]acetyl}-4-fluoro-2-pyrrolidinecarbonitrile

The title compound is prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and 2-pyridinecarboxaldehyde O-(4-amino-4-methylcyclohexyl)oxime obtained in Example 29-2 in a similar manner to that of Example 7-2.

Example 30-1

Nicotinaldehyde O-(4-amino-4-methylcyclohexyl)oxime

The title compound (171mg) was prepared from tert-butyl 1-methyl-4-({[(1E)-3-pyridinyl-methylidene]amino}oxy)cyclohexylcarbamate in a similar manner to that of Example 17-2.

MS (ESI+) : m/z 234.19 (M+H).

Example 30-2

(2S,4S)-1-{[(4-{[(3-pyridinylmethylidene)amino]oxy}-1-methylcyclohexyl)amino]acetyl}-4-fluoro-2-pyrrolidinecarbonitrile

The title compound is prepared from (2S,4S)-1-chloroacetyl-4-fluoro-2-pyrrolidinecarbonitrile obtained in Preparation 1-8 and nicotinaldehyde O-(4-amino-4-methyl-cyclohexyl)oxime obtained in Example 30-1 in a similar manner to that of Example 7-2.

In order to illustrate the usefulness of the object Compound (I), the pharmacological test is carried out as shown in the following.

[A] Inhibition test of human plasma DPP-IV :

(i) Material and Method :

The effect of test compounds on DPP-IV activity in human plasma was evaluated with a modified version of the assay described by Hughes et al (Biochemistry, 38, pp11597-11603(1999)).

Briefly, 20μL of human plasma were mixed with 20 μL of 80mM $MgCl_2$ in assay buffer (25mM HEPES, 140mM NaCl, 1% RIA-grade BSA, pH7.8), and were incubated in a room temperature for 60min. Then the reaction was initiated by the addition of both 20μL of test compounds and 20 μL of 0.2mM substrate (H-glycine-proline-AMC; AMC is 7-amino-4-methylcoumarine), they were dissolved in the assay buffer.

After 20min incubation in a room temperature (kept in the dark), fluorescence was measured (Excitation 380nm, Emission 460nm). A fluorescence-concentration curve of free AMC was obtained using AMC solution in the assay buffer with appropriate concentration. Plasma DPP-IV activities, with or without the test compounds, were expressed as the amount of product per minute per mL. The potency of the test compounds as DPP-IV inhibitor was expressed as IC_{50}.

(ii) Results :

The following IC_{50} values were obtained.

Table 1

Compound	IC_{50} value for human plasma DPP-IV (nM)
Example 1-6	14
Example 12-3	19
Example 22-3	21
Example 26-3	18
LAF 237	24

It appeared, from the above-mentioned Inhibition test, that the compound (I) and (1) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against DPP-IV.

Therefore, the compound (I) and (1) or pharmaceutically acceptable salts thereof are useful for treating or preventing disease mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

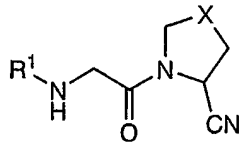
Further, the compound (I) and (1) or pharmaceutically acceptable salts thereof are useful for treating or preventing autoimmune disease, arthritis, rejection of transplanted organs, systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome (AIDS), hypertension, atherosclerosis, gallbladder disease, cancer, intestinal disease and dwarfism.

The patents, patent applications and publications cited herein are incorporated by reference.

This application is based on Australian Provisional Application No.2003902260 filed on May 9, 2003, the contents of which are hereby incorporated by references.

C L A I M S

1. A compound of the formula (I) or pharmaceutically acceptable salt thereof.

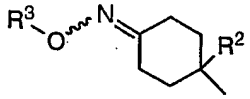


(I)

[wherein

X is CFH, or CF_2,

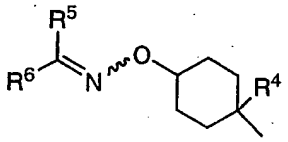
R^1 is the moiety represented by the formula:



[wherein R^2 is (lower)alkyl,

R^3 is cycloalkyl, aryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group)], or

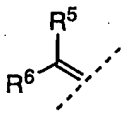
the moiety represented by the formula:



[wherein R^4 is (lower)alkyl,

R^5 is hydrogen, or (lower)alkyl,

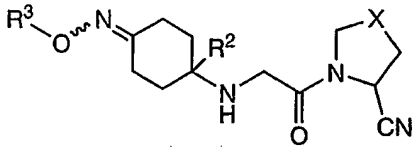
R^6 is (lower)alkyl, cycloalkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), and

the partial structure:  may form cycloalkylidene],

the "substituent(s)" is(are) selected from the group

consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy, halogen, cyano, nitro, amino and hydroxy]

2. A compound of the formula (II) or pharmaceutically acceptable salt thereof.



(II)

[wherein

X is CFH, or CF_2,

R^2 is (lower)alkyl,

R^3 is cycloalkyl, aryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower)alkyl (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group),

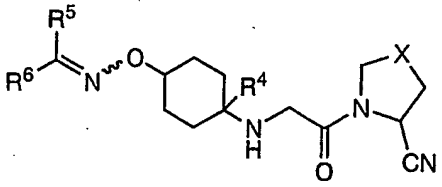
the "substituent(s)" is(are) selected from the group consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy, halogen, cyano, nitro, amino and hydroxy]

3. The compound of Claim 2, wherein X is CFH.

4. The compound of Claim 2 or 3, wherein R^2 is methyl.

5. The compound of any one of Claims 2 to 4, wherein R^3 is pyridinylmethyl (which may have 1 to 3 substituent(s)).

6. A compound of the formula (III) or pharmaceutically acceptable salt thereof.



(III)

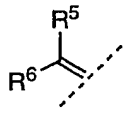
[wherein

X is CFH, or CF_2,

R^4 is (lower)alkyl,

R^5 is hydrogen, or (lower)alkyl,

R^6 is (lower)alkyl, cycloalkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), and

the partial structure:  may form cycloalkylidene,

the "substituent(s)" is(are) selected from the group consisting of (lower)alkyl, halogenated-(lower)alkyl, (lower)alkoxy, aryloxy, halogen, cyano, nitro, amino and hydroxy]

7. The compound of Claim 6, wherein X is CFH.

8. The compound of Claim 6 or 7, wherein R^4 is methyl.

9. The compound of any one of Claims 6 to 8, wherein R^5 is hydrogen.

10. The compound of any one of Claims 6 to 8, wherein R^5 is methyl.

11. The compound of any one of Claims 6 to 10, wherein R^6 is methyl.

12. The compound of any one of Claims 6 to 10, wherein R^6 is pyridinyl (which may have 1 to 3 substituent(s)).

13. The compound of any one of Claims 6 to 10, wherein R^6 is pyrimidinyl (which may have 1 to 3 substituent(s)).

14. A medicament comprising a compound of any one of Claims 1 to 13 as an active ingredient.

15. A pharmaceutical composition comprising a compound of any one of Claims 1 to 13 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

16. An inhibitor of DPP-IV consisting of a compound of any one of Claims 1 to 13.

17. A method for treatment and/or prevention of NIDDM which comprises administering an effective amount of the compound of any one of Claims 1 to 13 to human beings or animals.

18. The compound of any one of Claims 1 to 13 for use in the treatment and/or prevention of NIDDM in human beings or animals.

19. Use of the compound of any one of Claims 1 to 13 for the manufacture of a medicament for treatment and/or prevention of NIDDM in human beings or animals.

20. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in any one of Claims 1 to 13 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating NIDDM.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2004/006568

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D417/12 C07D207/16 C07D409/12 A61K31/4025

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/002523 A (BREED AUTOMOTIVE TECH) 9 January 2003 (2003-01-09) cited in the application page 6, line 5 - line 8 claim 1	1,14,19
A	NOVARTIS A G: "NOVEL N-SUBSTITUTED-2-CYANOPYRROLIDINES AS POTENT INHIBITORS OF DIPEPTIDYL PEPTIDASE IV IN THE TREATMENT OF NON-INSULIN-DEPENDENT DIABETES MELLITUS" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 10, no. 12, December 2000 (2000-12), pages 1937-1942, XP001019155 ISSN: 1354-3776 the whole document	1,14,19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 2004	15/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/006568

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP2004/006568

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03002523 A	09-01-2003	US 2003060997 A1	27-03-2003
		WO 03002523 A1	09-01-2003